Journal of Pharmaceutical Investigation (2013) 43:259–266
DOI 10.1007/s40005-013-0072-5

REVIEW

Drug release testing methods of polymeric particulate drug formulations

Sarmila Amatya · Eun Ji Park · Jong Hoon Park · Joon Sik Kim · Eunyoung Seol · Heeyong Lee · Hoil Choi · Young-Hee Shin · Dong Hee Na

Received: 4 March 2013 / Accepted: 23 April 2013 / Published online: 30 April 2013
© The Korean Society of Pharmaceutical Sciences and Technology 2013

Abstract The long-term controlled delivery of drugs has been successfully achieved by biodegradable polymeric particulate systems. The drug release testing method is important for the characterization of dosage form performance under in vitro standardized conditions and can provide insight into the in vivo performance of the drug product. In vitro drug release testing methods for polymeric particulate systems are classified into sample and separate (SS), dialysis, and continuous flow (CF) methods. In the SS method, the drug-loaded microparticles are suspended in a vessel and the samples for the analysis are obtained by separating the particles using filtration or centrifugation. The dialysis method physically separates microparticles from the release media by a membrane, which eliminates the undesired loss of particles during sample preparation and handling. The CF method uses apparatus consisted of flow-through cell that holds the sample, pump and water bath in closed or open ends system. In this method, the release media is continuously circulated through a cell containing drug-loaded microparticles. This review summarizes the principles of the drug release testing methods and discusses their characteristics with the recent research results.

Keywords In vitro drug release test · Microparticles · Sustained-release formulations

Introduction

Biodegradable polymeric particulate systems have been widely used for long-term controlled delivery of small synthetic molecules, peptides and proteins (Mundargi et al. 2008; Park et al. 2013; Wischke and Schwendeman 2008). Polylactide (PLA) and poly (lactide-co-glycolide) (PLGA) have been mainly adopted as a vehicle owing to their good biodegradability and biocompatibility (Gombotz and Pettit 1995; Anderson and Shive 1997; Park et al. 2005). The biodegradation of PLA and PLGA is useful for sustained drug release delivery at desirable doses by implantation without surgical procedures. In the numerous studies, PLA- or PLGA-based microparticles have been demonstrated as a highly promising carrier for sustained release delivery of several therapeutic agents (Klose et al. 2008; Choi et al. 2012). Since 1989, several biodegradable polymeric products, such as Lupron Depot, Sandostatin LAR, and Risperdal Consta, have been approved by Food and Drug Administration (FDA). A list of commercially available products is shown in Table 1.

To assure batch-to-batch reproducibility for consistent pharmacological effect, an appropriate product quality and performance (drug release) test is required. In the pharmaceutical industry, dissolution testing is powerful tool in both drug development and quality control purpose (Brown et al. 2011). This test is important for the characterization of dosage form performance under in vitro standardized

Sarmila Amatya and Eun Ji Park contributed equally to this study.

S. Amatya · Y.-H. Shin
College of Pharmacy, Kyungsung University, Busan 608-736, South Korea

E. J. Park · D. H. Na (✉)
College of Pharmacy and Research Institute of Pharmaceutical Sciences, Kyungpook National University, Daegu 702-701, South Korea
e-mail: dhna@knu.ac.kr

J. H. Park · J. S. Kim · E. Seol · H. Lee · H. Choi
Peptron, Inc., Daejeon 305-811, South Korea

Table 1 List of commercially available polymeric particulate drug products

Product (company)	Active ingredient	Polymer	Duration of action	Indication
Arestin (OraPharma)	Minocycline	PLGA	2 weeks	Periodontal disease
Bydureon (Amylin)	Exenatide	PLGA	1 week	Type 2 diabetes
Decapeptyl SR (Ferring/Ipsen)	Triptorelin	PLGA	1, 3 months	Prostate cancer
Lupron Depot (TAP)	Leuprolide	PLGA	1, 3, 4 months	Prostate cancer
Risperdal Consta (Janssen)	Risperidone	PLGA	2 weeks	Schizophrenia
Sandostatin LAR (Novartis)	Octreotide	PLGA-glucose	1 month	Acromegaly
Somatuline PR (Ipsen)	Lanreotide	PLGA	1 month	Acromegaly
Suprecur MP (Sanofi-Aventis)	Buserelin	PLGA	1 month	Prostate cancer
Vivitrol (Alkermes)	Naltrexone	PLGA	1 month	Alcoholism

conditions and can provide insight into the in vivo performance of the drug product (Mitra and Wu 2010). For orally administered immediate release solid drug products, it is usually refer as a dissolution test, since the drug is intended to dissolve rapidly in the test medium. For non-oral dosage forms such as topical and transdermal delivery systems, suppositories, and others, the test is referred to preferably as a drug release or in vitro release test procedure (Brown et al. 2011).

Drug release from polymeric microparticles typically shows a triphasic profile controlled by diffusion and erosion: initial release of drugs at or near the microparticle surface, a lag time during erosion phase of microparticles, and drug release on bulk erosion of the microparticles. For continuous drug release, the diffusion and erosion processes must be complementary to allow the drug to constantly diffuse out of the microparticles (Cleland 1995). As the drug release profiles from polymeric microparticles can range from days to months, the long test time and the high cost are required (Mitra and Wu 2010). Unlike controlled release oral formulations, no regulatory standards have been established for in vitro release method of injectable polymeric microparticles (D'Souza and DeLuca 2006). This review introduces characteristics of the drug release testing methods and discusses their advantages, disadvantages, and applications.

Drug release testing methods of injectable polymeric microparticles

The current United States Pharmacopeia (USP) apparatus for in vitro drug release testing was designed for oral and transdermal products and is not directly applicable for parenteral polymeric products (Mitra and Wu 2010). USP apparatuses 1 (basket) and 2 (paddle) have been mainly used for oral dosage forms such as tablet and capsule, and USP apparatuses 3 (reciprocating cylinder) and 4 (flow-through cell) were specifically designed for extended-release oral dosage forms. USP apparatuses 5 (paddle over disk), 6 (rotating cylinder) and 7 (reciprocating holder) are used for the dosage forms using the transdermal route. Although the application of the testing methods has recently expanded to a variety of novel or special dosage forms, the drug release testing methods of polymeric microparticulate systems do not use an official USP dissolution/release apparatus. In recognition of the requirement of a standard in vitro release method for polymeric microparticulate systems, FIP/AAPS Joint Workshop report on "Dissolution/in vitro release testing of novel/special dosage forms" published important guidelines for novel or special dosage forms, including chewing gums, microparticulate formulations, and implants (Brown et al. 2011). These delivery systems were categorized as those dosage forms for "more work needed before recommendation".

Recently, D'Souza and DeLuca (2006) classified the in vitro drug release testing methods for polymeric microparticulate systems into sample and separate (SS), dialysis, and continuous flow (CF) methods. Figure 1 shows basic principles of three types of in vitro drug release testing methods, SS method, dialysis method, and CF method (Larsen et al. 2009).

Sample and separate methods (SS)

This method is the most common and popular method for in vitro release testing of polymeric particulate products mainly due to its simplicity and practicability. In general, drug-loaded microparticles are suspended in a vessel containing certain amount of release media and then the drug release is assessed over time. Many researchers used this method for the drug release study from microparticles by adjustment of various parameters such as size of container, types of agitation, sample separation technique and sampling volume (D'Souza and DeLuca 2006).

The type of container is selected depending on the volume of media necessary for release study. In general, tubes or bottles have been adopted when small volumes of

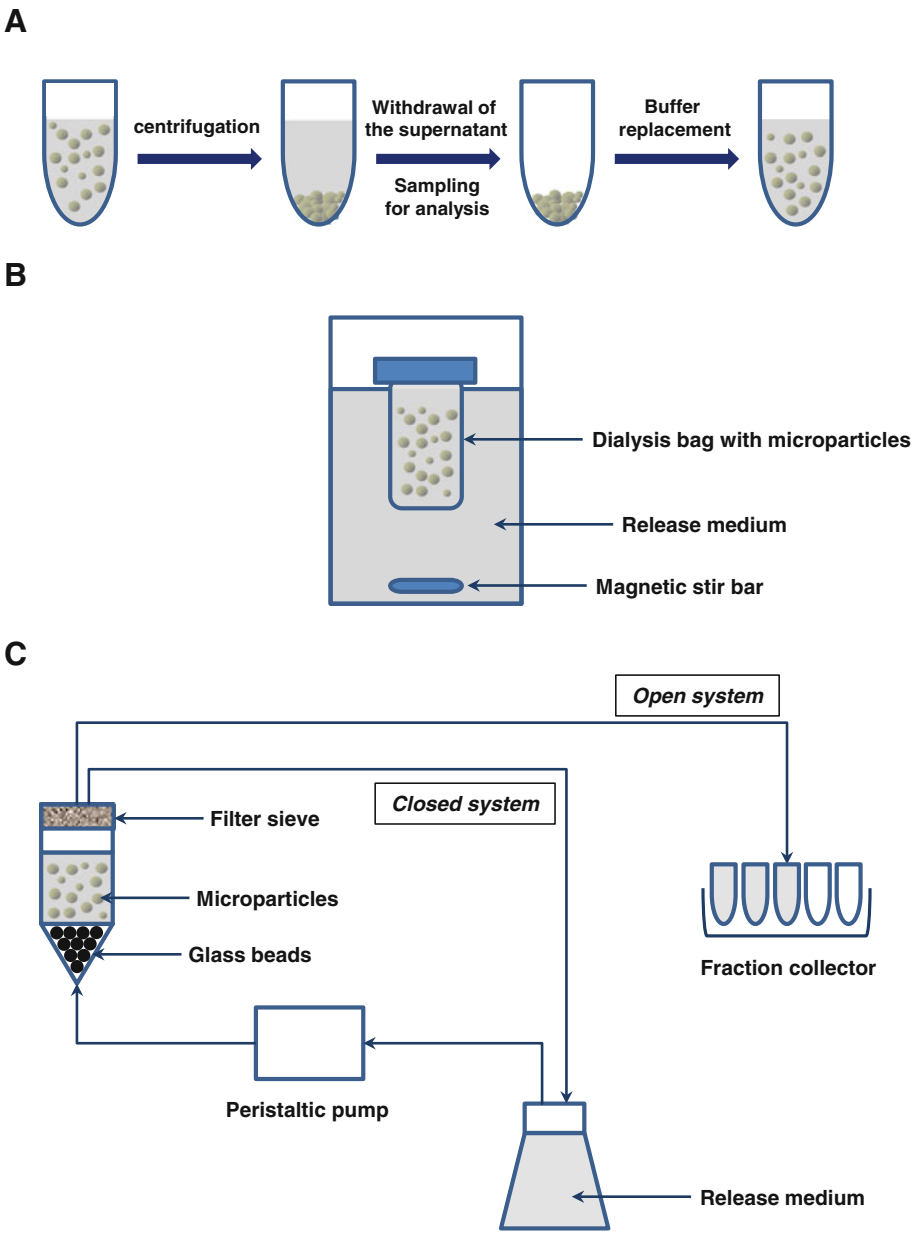

Fig. 1 Basic principles of in vitro drug release testing methods, **a** sample and separate method, **b** dialysis method, and **c** continuous flow method with open or closed system (Modified from Larsen et al. 2009)

media less than 10 mL are used (Yang et al. 2000; Xu et al. 2009) and bottles or flasks have been used when large volumes (100–400 mL) are required (Yen et al. 2001; Jeong et al. 2003). Once drug-loaded microparticles are suspended in media, it may be subjected to continuous or intermittent agitation during the release study. There are various means to integrate agitation depending upon the availability and compatibility. It includes continuous rotation using wrist shaker (Murty et al. 2003), shaking in water bath or incubator (Kim and Burgess 2002), and tumbling end-over-end (Liggins and Burt 2001). At the predetermined time interval, the sample for the analysis can be obtained by separating the particles using filtration or centrifugation. Filtration is carried out using membrane filters with appropriate pore size that can filter polymeric materials. Centrifugation is more popular method and is followed by sampling of the supernatant or analysis of remaining drug in the microspheres. Instead of sampling, total particulate removal and analysis at predetermined time interval can be alternatively used (Park et al. 2007), but this requires a large amount of microparticles and high manufacturing cost. In some case, method that allows microparticles to settle and then sampling from the top of the media has been reported (Bodmeier and McGinity 1987). After sampling, buffer replacement is necessary to maintain the sink condition. After buffer replacement, the centrifuged samples are resuspended for continuing release study (Wei et al. 2004).

Various modifications of the SS method have been employed to assess in vitro drug release. Xu et al. (2009) used the SS method for obtaining in vitro release profiles of bupivacaine from monodisperse polymeric microparticles prepared using a microfluidic flow-focusing device. In this method, 1 mg of bupivacaine-loaded PLGA microspheres were suspended in 1 mL of 0.9 % NaCl solution in a 1.5-mL centrifuge tube and incubated at 37 °C on a tilt-table. At predetermined intervals, the tube was centrifuged at 12000 rpm for 5 min, supernatant layer was removed for analysis, and an equal volume of fresh 0.9 % NaCl solution was added to the tube. The amount of bupivacaine in the supernatant was determined by HPLC analysis.

Murty et al. (2005) used the SS method for investigating release profiles and impurity formation of octreotide-loaded PLA or PLGA microspheres. In this study, 15 mg of microspheres were suspended into 4 mL of 20 mM phosphate buffered saline in 15 mL-sized polypropylene tubes and the samples were continuously agitated at 100 rpm in a shaking air bath at 37 °C. At predetermined intervals, the tubes were centrifuged to facilitate the removal of buffer and the microspheres were then resuspended with 4 mL of fresh buffer by vortexing. The supernatant samples were analyzed by HPLC.

Guerrero et al. (2008) prepared ketotifen-loaded PLA and PLGA microspheres by spray-drying technique. For drug release studies, 30 mg of microspheres was introduced into the container containing 50 mL of phosphate buffer. The samples were placed in an orbital incubator at a constant shake (200 rpm). At predetermined intervals, 1 mL of samples were withdrawn and assayed by using UV spectrophotometry at 297 nm.

Ahmed et al. (2012) studied biodegradable injectable in situ implant and in situ microparticle formulations for sustained delivery of haloperidol. In this study, in vitro release test was done by introducing 25 mg of microsphere to 900 mL of phosphate buffer saline (PBS) in a closed-top 1000 mL bottle. The bottles were stored in the environmental shaker at 37 °C with moderate shaking at 50 rpm. At regular intervals, supernatant of each bottle was collected and analyzed using an UV spectrophotometer at 247 nm. Similarly Tunçay et al. (2000) used the SS method for in vitro–in vivo evaluation of diclofenac sodium-incorporated PLGA microspheres, in which 50 mg of microspheres were introduced in 50 mL glass vial containing 25 mL of PBS (pH 6.8) and shaken at 50 rpm in a thermostated bath at 37 °C. At predetermined time intervals, samples were withdrawn, filtered, and assayed by UV spectrophotometry.

Schoubben et al. (2012) investigated influence of agitation regimen in the SS method on the in vitro release behavior of leuprolide from PLGA microspheres. In this study, the in vitro release study was performed in 10 mL of 0.1 M phosphate buffer (pH 7.4) under continuous or once-a-week magnetic agitation (1 min duration). At predetermined intervals, drug release, polymer mass loss, and degree of hydration were investigated. The drug release and polymer mass loss were higher under continuous agitation with respect to that under once-a-week agitation. This work indicated the importance of the in vitro release conditions on drug release behavior from PLGA microparticles.

Dialysis methods

Dialysis methods are also widely used method for in vitro release testing of microparticles. In these methods, drug-loaded microparticles are physically separated from the bulk media by a dialysis membrane bag of certain molecular-weight cut-off (MWCO) and drug release is generally assessed from the outer bulk over time. The media is selected based on drug solubility and stability over the duration of the release study. The dialysis method has been widely used to investigate drug release from oil-based injectable depots (Schultz et al. 1997; Larsen et al. 2002), particulate formulations of poorly water-soluble drugs (Parshad et al. 2003), liposomes (Xu et al. 2012), and nanoparticles (Asadishad et al. 2010).

Dialysis methods include rotating dialysis cell (dialysis sac method) or reverse dialysis sac method. In rotating dialysis cell, the suspension of microparticle is placed in the dialysis membrane bag or the sample may be placed into tube where only one end bears a dialysis membrane. The dialysis sac method eliminated the undesired loss of microspheres during sample preparation and handling because the media and the particles are already physically separated by a membrane, and the sampling and media replacement are easy (D'Souza and DeLuca 2006). Key parameters influencing the drug release in dialysis method include agitation conditions, ratio between donor and receptor cell volume, and MWCO of dialysis membrane. It has been recommended that the dialysis membrane should be 100 times the size of drug molecules. It was also suggested to maintain the volume of the microparticulate suspension 5–10 times less than the bulk media to maintain sink conditions. Although the dialysis method offers several advantages like ease of sample withdrawal, physical separation of microparticles from buffer and convenience, this technique cannot be used if the drug binds to the polymer or dialysis membrane (Kinget et al. 1979). In some cases, drug may be unstable in the media and it requires the sacrificing of microspheres followed by analysis of the remaining drug.

Reverse dialysis method is similar to dialysis sac method except the drug is placed outside the dialysis sac

and sampling is done inside the dialysis sac containing only media either by opening the dialysis sac and removing the certain amount media or by removing the whole dialysis sac and replacing with the new one (Maestrelli et al. 2004; Xu et al. 2012). The main advantage of this method is that agitation of suspension of microparticle instead of bulk media prevents the aggregation of particle and avoids the violation of sink condition that occur in dialysis sac method. However, this method also has disadvantages like loss of sample especially in case of injection or emulsion.

D'Souza and DeLuca (2005) developed a simple and convenient in vitro release method for PLGA microspheres using a commercially available dialyzer, 25 KD MWCO Float-a-Lyzer. In vitro release of leuprolide from PLGA microspheres was assessed using the dialyzer and compared with the SS method with and without agitation. In the dialysis method, 50 mg of leuprolide-loaded microspheres were transferred to the dialyzer and suspended in 5 mL release media. The dialyzer was then introduced into a 5 mL glass cylinder containing release media, which was stirred at 300 rpm using a magnetic stirrer. Drug release was assessed by sampling the contents of the outer media. As the membrane was stable to elevated temperatures, it could be used for accelerated release study in which high temperatures are used.

D'Souza et al. (2005) used dialysis method to develop accelerated in vitro release testing to correlate or predict long-term in vitro release of leuprolide-loaded PLGA microspheres at 37 °C and at elevated temperatures (50–60 °C). In vitro release profiles at the elevated temperatures correlated well with release at 37 °C.

Recently, Xu et al. (2012) developed a novel two-stage reverse dialysis method for in vitro release testing of liposomal drug product. The first stage of the test is to mimic the circulation of liposomes in the body, whereas the second stage is to imitate the drug release process at the target. Buffer and surfactant solution were used during the first and second stages, respectively. Among two different membrane diffusion techniques, dialysis and reverse dialysis methods, the reverse dialysis method showed significantly lower variation. The developed in vitro release testing method would be valuable for quality control testing purposes.

Continuous flow methods (CF)

Continuous flow apparatus consists of flow-through cell that holds the sample, pump and water bath in closed or open ends system. In closed system, media is continuously circulated through a column containing drug-loaded microparticles, and release is assessed over a period of time (Wagenaar and Müller 1994; Wang et al. 2002). In open system, a fraction collector is attached and media only passes through cell one time (Rawat et al. 2012). Modifications of the USP apparatus for CF methodology have been achieved with proper adjustment of the parameters such as media, pumps, and flow rate. A modified USP apparatus 4 method for in vitro release testing of microspheres under real time and accelerated testing conditions has been developed with the advantages of the USP apparatus 4 method over the SS methods (Zolnik et al. 2006; Voisine et al. 2008). Modified USP apparatus 4 method offers several advantages such as separation of microspheres from the release medium, ease of operation, minimum evaporation of the media, flexibility of monitoring release via in situ fiber optics, and automation (Rawat et al. 2011; Shen and Burgess 2012). In addition, aggregation of the hydrophobic microspheres, loss of microspheres during sampling and media replacement and operator variability could be minimized.

In the CF method, several pumps, such as peristaltic (Wagenaar and Müller 1994; Vandelli et al. 2001), syringe (Aubert-Pouëssel et al. 2004) and HPLC pump (Wang et al. 2002), have been used for the constant flow of the system. According to the pump type, different flow rates have been used. Syringe pumps have been used at a flow rate of 5 μL/min (Aubert-Pouëssel et al. 2004), HPLC pumps at 0.4 mL/min, and peristaltic pumps at 3–30 mL/min (Wagenaar and Müller 1994; Conti et al. 1995). When the CF method is used, the flow rate is an important parameter in the assessment of drug release because low flow rates can result in slow and incomplete release due to insufficient transfer of the release media. The use of HPLC pumps may be considered to provide the necessary accuracy and precision at very low flow rates.

Zolnik and Burgess (2008) used USP apparatus 4 for in vitro testing of dexamethasone-loaded PLGA microspheres. In this study, in vitro release studies were conducted using a modified USP apparatus 4 with flow-through cells (12 mm diameter) packed with glass beads (1 mm) (to prevent microsphere agglomeration and to achieve laminar flow) in a closed system mode. 45 mg of microspheres were dispersed in the flow-through cells and 250 mL of 0.1 M PBS (pH 7.4) was circulated through a fiberglass filter (0.45 μm) with a flow rate of 20 mL/min.

Rawat et al. (2011) validated USP apparatus 4 method for in vitro release testing of risperidone microspheres product, Risperdal Consta. A USP apparatus 4 method was validated in real-time release condition (37 °C) and accelerated conditions (45 °C). The robustness testing study found that release from the microspheres was not dependent on the flow rate and was not affected by minor variations in the method, such as cell preparation technique, amount of microspheres, size of the flow-through cell and size of glass beads. However, small variations in

Table 2 Characteristics of in vitro drug release testing methods (D'Souza and DeLuca 2006)

	Sample and separate method	Dialysis method	Continuous flow method
Sample container	Tube or vial	Dialysis bag	Flow-through cell
Sampling	Isolation of microparticles by filtration or centrifugation	Withdrawal of sample from the bulk media outside the membrane	Media is circulated through the cell containing the microparticles and the media is sampled from the reservoir
Advantages	Accurate measurement of the initial burst drug release and maintenance of sink conditions by replacement of the release media	Sampling and media replacement are convenient owing to a physical separation of the microparticles from the outer media	Samples can be continuously collected and analyzed via the automated process. Analysis of multiple time points can allow for complete characterization of the release profile
Disadvantages	Cumbersome sampling process and undesirable withdrawal of microparticles from the media	Slow equilibration with the outer media limits an accurate measurement of initial drug levels	Variation in the flow rate due to clogging of the filter and difficulty in rapid replacement of the media

temperature resulted in the significant difference in the release profile. Rawat et al. (2012) also used USP apparatus 4 method for investigating the relationship between in vitro and in vivo release of Risperdal Consta microspheres. In this study, the accelerated tests performed at temperature above the microspheres Tg were proposed to be useful for in vitro–in vivo correlation study and quality control of risperidone microspheres.

Rawat and Burgess (2011) developed USP apparatus 4 method for in vitro release study of protein-loaded PLGA microspheres. In this study, a modified USP apparatus 4 was compared with the SS method using a microsphere formulation encapsulating bovine serum albumin (BSA). In the SS method, incomplete release of BSA was observed due to microsphere loss during sampling. The modified USP apparatus 4 method eliminated this problem. To prevent BSA adsorption onto the hydrophobic surfaces of the modified USP apparatus 4, SDS was added to the release media and a zero order release profile was obtained.

Characteristics of in vitro drug release testing methods

Table 2 summarizes the characteristics of in vitro drug release testing methods for polymeric particulate systems. Among three in vitro drug release testing methods, the most common and simple method is SS method, often referred to as tube method. This method is advantageous for measuring initial burst release and maintaining sink conditions by replacement of the release media. However, the cumbersome sampling technique and undesirable withdrawal of particles from the media are disadvantages. Dialysis methods are also commonly used method for in vitro release testing of microparticles. The dialysis method eliminates the undesired loss of particles during sample preparation and handling because the media and the particles are already physically separated by a membrane. In addition, the sampling and media replacement are more convenient. Disadvantages of this method are that slow equilibration with outer media may limit an accurate analysis of initial drug levels in formulations where the burst release is high and it cannot be used if the drug binds to the polymer or dialysis membrane. In some cases, drug may be unstable in the media. The CF method uses apparatus consisted of flow-through cell that holds the sample, pump and water bath in closed or open ends system. A modified USP apparatus 4 method has been used in several studies and it offers several advantages such as separation of microspheres from the release medium, ease of operation, minimum evaporation of the media, flexibility of monitoring drug release via in situ fiber optics, and automation. In addition, aggregation of the hydrophobic microspheres, loss of microspheres during sampling and media replacement and operator variability can be minimized. Disadvantages of this method include variation in the flow rate due to clogging of the filter and difficulty in rapid replacement of the release media.

Conclusions

Sustained-release parenteral drug products have been developed to appropriately deliver therapeutic agents for the treatment and prevention of a variety of diseases. Many studies have been performed for discovery and preparation of novel materials and formulations, but relatively limited attention has been dedicated to the development of appropriate in vitro release testing methods of sustained-release formulations. This drug release testing method is important for the characterization of dosage form performance under in vitro standardized conditions and it can provide insight into the in vivo performance of the drug product. In vitro drug release testing methods for polymeric particulate systems are generally classified into SS,

dialysis, and CF methods. These methods have individual advantages and disadvantages, and they can be controlled by several factors. Therefore, it is difficult to seek a single in vitro drug release testing methods for all the formulations. For the development of reliable drug release testing methods, the attempts to optimize the detailed aspects of methodologies are more necessary.

Acknowledgments This research was financially supported by the Ministry of Knowledge Economy (MKE) and Korea Institute for Advancement in Technology (KIAT) through the Research and Development for Regional Industry. This research was also supported by the leading industry and equipments of the ChungCheong Leading Industry Office of the Korean Ministry of Knowledge.

References

Ahmed TA, Ibrahim HM, Ibrahim F, Samy AM, Kaseem A, Nutan MT, Hussain MD (2012) Development of biodegradable in situ implant and microparticle injectable formulations for sustained delivery of haloperidol. J Pharm Sci 101:3753–3762

Anderson JM, Shive MS (1997) Biodegradation and biocompatibility of PLA and PLGA microspheres. Adv Drug Deliv Rev 28:5–24

Asadishad B, Vossoughi M, Alamzadeh I (2010) In vitro release behavior and cytotoxicity of doxorubicin-loaded gold nanoparticles in cancerous cells. Biotechnol Lett 32:649–654

Aubert-Pouëssel A, Venier-Julienne MC, Clavreul A, Sergent M, Jollivet C, Montero-Menei CN, Garcion E, Bibby DC, Menei P, Benoit JP (2004) In vitro study of GDNF release from biodegradable PLGA microspheres. J Control Release 95: 463–475

Bodmeier R, McGinity JW (1987) The preparation and evaluation of drug-containing poly(DL-lactide) microspheres formed by the solvent evaporation method. Pharm Res 4:465–471

Brown CK, Friedel HD, Barker AR, Buhse LF, Keitel S, Cecil TL, Kraemer J, Morris JM, Reppas C, Stickelmeyer MP, Yomota C, Shah VP (2011) FIP/AAPS joint workshop report: dissolution/in vitro release testing of novel/special dosage forms. AAPS PharmSciTech 12:782–794

Choi JS, Seo K, Yoo JW (2012) Recent advances in PLGA particulate systems for drug delivery. J Pharm Invest 42:155–163

Cleland JL (1995) Design and production of single immunization vaccines using polylactide polyglycolide microsphere systems. In: Powell MF, Newman MJ (eds) Vaccine Design. Plenum, New York, pp 439–472

Conti B, Genta I, Giunchedi P, Modena T (1995) Testing of "in vitro" dissolution behavior of microparticulate drug delivery systems. Drug Dev Ind Pharm 21:1223–1233

D'Souza SS, DeLuca PP (2005) Development of a dialysis in vitro release method for biodegradable microspheres. AAPS PharmSciTech 6:E323–E328

D'Souza SS, DeLuca PP (2006) Methods to assess in vitro drug release from injectable polymeric particulate systems. Pharm Res 23:460–474

D'Souza SS, Faraj JA, DeLuca PP (2005) A model-dependent approach to correlate accelerated with real-time release from biodegradable microspheres. AAPS PharmSciTech 6:E553–E564

Gombotz WR, Pettit DK (1995) Biodegradable polymers for protein and peptide drug delivery. Bioconjug Chem 6:332–351

Guerrero S, Muñíz E, Teijón C, Olmo R, Teijón JM, Blanco MD (2008) Ketotifen-loaded microspheres prepared by spray-drying poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) polymers: characterization and in vivo evaluation. J Pharm Sci 97: 3153–3169

Jeong YI, Song JG, Kang SS, Ryu HH, Lee YH, Choi C, Shin BA, Kim KK, Ahn KY, Jung S (2003) Preparation of poly(DL-lactide-co-glycolide) microspheres encapsulating all-trans retinoic acid. Int J Pharm 259:79–91

Kim H, Burgess DJ (2002) Effect of drug stability on the analysis of release data from controlled release microspheres. J Microencapsul 19:631–640

Kinget R, Bontinck AM, Herbots H (1979) Problems of dialysis techniques in the study of macromolecule binding of drugs. Int J Pharm 3:65–72

Klose D, Siepmann F, Elkharraz K, Siepmann J (2008) PLGA-based drug delivery systems: importance of the type of drug and device geometry. Int J Pharm 354:95–103

Larsen DB, Joergensen S, Olsen NV, Hansen SH, Larsen C (2002) In vivo release of bupivacaine from subcutaneously administered oily solution. Comparison with in vitro release. J Control Release 81:145–154

Larsen C, Larsen SW, Jensen H, Yaghmur A, Ostergaard J (2009) Role of in vitro release models in formulation development and quality control of parenteral depots. Expert Opin Drug Deliv 6:1283–1295

Liggins RT, Burt HM (2001) Paclitaxel loaded poly(L-lactic acid) microspheres: properties of microspheres made with low molecular weight polymers. Int J Pharm 222:19–33

Maestrelli F, Mura P, Alonso MJ (2004) Formulation and characterization of triclosan sub-micron emulsions and nanocapsules. J Microencapsul 21:857–864

Mitra A, Wu Y (2010) Use of in vitro–in vivo correlation (IVIVC) to facilitate the development of polymer-based controlled release injectable formulation. Recent Pat Drug Deliv Formul 4:94–104

Mundargi RC, Babu VR, Rangaswamy V, Patel P, Aminabhavi TM (2008) Nano/micro technologies for delivering macromolecular therapeutics using poly(D,L-lactide-co-glycolide) and its derivatives. J Control Release 125:193–209

Murty SB, Goodman J, Thanoo BC, DeLuca PP (2003) Identification of chemically modified peptide from poly(D,L-lactide-co-glycolide) microspheres under in vitro release conditions. AAPS PharmSciTech 4:E50

Murty SB, Na DH, Thanoo BC, DeLuca PP (2005) Impurity formation studies with peptide-loaded polymeric microspheres Part II. In vitro evaluation. Int J Pharm 297:62–72

Park EJ, Na DH, Lee KC (2007) In vitro release study of mono-PEGylated growth hormone-releasing peptide-6 from PLGA microspheres. Int J Pharm 343:281–283

Park JH, Ye M, Park K (2005) Biodegradable polymers for microencapsulation of drugs. Molecules 10:146–161

Park EJ, Amatya S, Kim MS, Park JH, Seol E, Lee H, Shin YH, Na DH (2013) Long-acting injectable formulations of antipsychotic drugs for the treatment of schizophrenia. Arch Pharm Res. doi: 10.1007/s12272-013-0105-7

Parshad H, Frydenvang K, Liljefors T, Cornett C, Larsen C (2003) Assessment of drug salt release from solutions, suspensions and in situ suspensions using a rotating dialysis cell. Eur J Pharm Sci 19:263–272

Rawat A, Burgess DJ (2011) USP apparatus 4 method for in vitro release testing of protein loaded microspheres. Int J Pharm 409:178–184

Rawat A, Stippler E, Shah VP, Burgess DJ (2011) Validation of USP apparatus 4 method for microsphere in vitro release testing using Risperdal Consta. Int J Pharm 420:198–205

Rawat A, Bhardwaj U, Burgess DJ (2012) Comparison of in vitro–in vivo release of Risperdal Consta microspheres. Int J Pharm 434:115–121

Schoubben A, Blasi P, Deluca PP (2012) Effect of agitation regimen on the in vitro release of leuprolide from poly(lactic-co-glycolic) acid microparticles. J Pharm Sci 101:1212–1220

Schultz K, Møllgaard B, Frokjaer S, Larsen C (1997) Rotating dialysis cell as in vitro release method for oily parenteral depot solutions. Int J Pharm 157:163–169

Shen J, Burgess DJ (2012) Accelerated in vitro release testing of implantable PLGA microsphere/PVA hydrogel composite coatings. Int J Pharm 422:341–348

Tunçay M, Caliş S, Kaş HS, Ercan MT, Peksoy I, Hincal AA (2000) Diclofenac sodium incorporated PLGA (50:50) microspheres: formulation considerations and in vitro/in vivo evaluation. Int J Pharm 195:179–188

Vandelli MA, Rivasi F, Guerra P, Forni F, Arletti R (2001) Gelatin microspheres crosslinked with D,L-glyceraldehyde as a potential drug delivery system: preparation, characterisation, in vitro and in vivo studies. Int J Pharm 215:175–184

Voisine JM, Zolnik BS, Burgess DJ (2008) In situ fiber optic method for long-term in vitro release testing of microspheres. Int J Pharm 356:206–211

Wagenaar BW, Müller BW (1994) Piroxicam release from spray-dried biodegradable microspheres. Biomaterials 15:49–54

Wang J, Wang BM, Schwendeman SP (2002) Characterization of the initial burst release of a model peptide from poly(D,L-lactide-co-glycolide) microspheres. J Control Release 82:289–307

Wei G, Pettway GJ, McCauley LK, Ma PX (2004) The release profiles and bioactivity of parathyroid hormone from poly(lactic-co-glycolic acid) microspheres. Biomaterials 25:345–352

Wischke C, Schwendeman SP (2008) Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles. Int J Pharm 364:298–327

Xu Q, Hashimoto M, Dang TT, Hoare T, Kohane DS, Whitesides GM, Langer R, Anderson DG (2009) Preparation of monodisperse biodegradable polymer microparticles using a microfluidic flow-focusing device for controlled drug delivery. Small 5: 1575–1581

Xu X, Khan MA, Burgess DJ (2012) A two-stage reverse dialysis in vitro dissolution testing method for passive targeted liposomes. Int J Pharm 426:211–218

Yang YY, Chia HH, Chung TS (2000) Effect of preparation temperature on the characteristics and release profiles of PLGA microspheres containing protein fabricated by double-emulsion solvent extraction/evaporation method. J Control Release 69:81–96

Yen SY, Sung KC, Wang JJ, Yoa-Pu Hu O (2001) Controlled release of nalbuphine propionate from biodegradable microspheres: in vitro and in vivo studies. Int J Pharm 220:91–99

Zolnik BS, Burgess DJ (2008) Evaluation of in vivo–in vitro release of dexamethasone from PLGA microspheres. J Control Release 127:137–145

Zolnik BS, Leary PE, Burgess DJ (2006) Elevated temperature accelerated release testing of PLGA microspheres. J Control Release 112:293–300