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ORIGINAL ARTICLE

Standardized in vitro drug release test for colloidal drug carriers using modified USP dissolution apparatus I

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Abstract

Background: Recently the use of colloidal carriers as drug delivery systems is gaining more attention. Evaluation of the in vitro drug release is considered an important step during the development and quality control of such systems. Therefore, there is a need for a standard test technique to study in vitro drug release from colloidal systems. *Methods*: The glass basket dialysis method was performed by a modification to the USP dissolution apparatus I by replacing the baskets with glass cylinders closed at the lower end by dialysis membrane. This method was characterized for the essential test parameters and compared to the dialysis bags technique using different types of colloidal drug carriers, namely liposomes, polymeric, and lipid nanoparticles. *Results*: The method proved to be more discriminating than the conventional dialysis bag method and allowed for better comparison between different formulation parameters or experimental conditions. In general, the design is easy to perform, simple, and available in all pharmaceutical laboratories under the same setup. *Conclusion*: The described method is a step toward standardized dissolution tests on colloidal drug delivery systems and the possible comparability of results.

Key words: Dialysis, in vitro drug release, liposomes, modified dissolution tester, nanoparticles

Introduction

In vitro drug release testing is an important tool in the quality control of drug delivery systems and it can be used as well for the prediction of in vivo drug kinetics. Because of the very small size of colloidal drug carriers, researchers are always facing technical problems during the in vitro drug release evaluation from these nano-sized systems. These obstacles consist in the separation of dispersed and continuous phases in a rapid and efficient way[1].

Various methods have been proposed to study the in vitro drug release from colloids which have been intensively reviewed by Washington[2]. These methods can be divided into four broad categories which are membrane diffusion techniques, sample and separate techniques, in situ methods, and continuous flow methods. Sample and separate methods depend mainly on diluting the colloidal suspension directly with the release medium and then sampling at different time intervals. Ultrafiltration, ultracentrifugation, or the centrifugal ultrafiltration techniques are then used to separate the dispersed particles from the continuous phase to analyze released drug concentration in the supernatant. Because of the very small size of nano-sized carriers, it is very difficult to separate them cleanly and sufficiently rapid without influencing the release profile.

This appears even more important in the context that the development of new colloidal drug carriers results more and more in particles distinctly smaller than 100 nm.

The application of strong centrifugal or filtration force to separate the particles may affect the integrity of the system especially in the case of very flexible carriers such as liposomes and nanoemulsions and thus interfering with drug release results. Also, long centrifugation times can have an impact on the results as drug carriers continue releasing in the meanwhile.

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The in situ methods are depending on diluting the particles into sink conditions and the released drug is determined by special analytical procedures without separating the carrier from the drug. This is valid only in case of drugs detected by polarography[3] or by spectroscopy[4] and is not affected by the presence of colloidal particles in solution which can be only ensured in very few cases.

Continuous flow methods are performed by constantly pumping a small volume of media through immobilized particles then passing through filter to analyze the drug content. Problems associated with filter clogging leading to lowering the flow rate and high pressure buildup in the system are common. Also it is practically difficult to achieve rapid replacement of the buffer[5].

Membrane diffusion techniques are considered the best for assessing the in vitro drug release from nanoparticles. In these techniques the colloidal carrier is separated from the sink release medium by dialysis membrane which is permeable to the drug. This method has been criticized by Washington as the carrier system itself is not diluted to the sink condition so the drug release rate is going to be mainly affected by the drug partitioning between the continuous phase in the donor compartment and the bulk phase in the receptor compartment. However, this effect can be reduced to a minimum by using large pore size membranes. The method is widely utilized for the in vitro drug release testing and satisfactory results are obtained as the drug release experiments can be viewed in most of the cases as a partitioning phenomenon[6–10]. Considering the hindrance to drug diffusion caused by dialysis bags, the release of the drug in solution form can be studied through the dialysis bag and any diffusional barrier can be compensated for[11]. A reverse dialysis technique has been proposed to avoid this criticism where the colloidal particles suspension can be directly diluted with the release medium and dialysis bags containing the release medium are then added and analyzed at different time intervals for drug content[12]. However, the method was not sensitive for the fast-releasing formulations and could not clearly discriminate the difference between release behavior from different types of colloidal carriers[13].

In the present work, we tried to standardize the membrane diffusion technique by using a modification of the standard USP dissolution testing method designing glass baskets as donor compartment separated from the receptor medium by a dialysis membrane providing a constant surface area for the drug release. The different main test conditions were characterized for their influence. The glass basket dialysis (GBD) method has been compared to the dialysis bags technique using different types of colloidal carriers namely liposomes, polymeric, and lipid nanoparticles. Diverse formulations were analyzed for their release elucidating potential differences compared to the conventional dialysis membrane technique.

Materials and methods

Materials

Ibuprofen and Solutol® HS15 (Polyethylene glycol – 660 hydroxystearate) were kind samples from BASF (Ludwigshafen, Germany). Ethyl cellulose (Ethocel standard 4 premium) was a gift from Colorcon, Dartford, England. Miglyol® 812 (medium-chain triglyceride) was from Fagron GmbH (Barsbüttel, Germany). Soybean lecithin was purchased from Caelo, Hilden, Germany. Spectra/Por® regenerated cellulose dialysis membrane, molecular weight cut off 12–14 and 50 KDa, were purchased from Spectrum Laboratories Inc., Rancho Dominguez, Canada. Cuprophan Type RC49–80 M regenerated cellulose membrane (MWCO 15–25 KDa) was obtained from Akzo Nobel, Wuppertal, Germany. All other chemicals were of analytical grade or equivalent quality.

Preparation of the different nanoparticles

For the preparation of liposomes, 100 mg of lecithin and 25 mg of ibuprofen were dissolved in 5 mL of ethanol. The solution was then evaporated under reduced pressure till complete vaporization of ethanol leaving a thin lipid film, which was then rehydrated with 5 mL distilled water. The mixture was sonicated for 30 minutes and then extruded through a 100 nm polycarbonate membrane.

The preparation of polymeric nanoparticles was done by O/W emulsion homogenization technique[6]. Simply, 50 mg (or 20 mg) of ibuprofen were dissolved in 3 mL dichloro-methane containing 100, 200, 500 mg of the polymer Ethocel®4. This organic solution was then poured into 10 mL of 0.5% PVA aqueous solution and the coarse emulsion formed was further homogenized with an ultrasonic cell disruptor (Banoelin sonopuls, Berlin, Germany) for 4 minutes. Solvent evaporation was then performed at room temperature in a Buchi Rotavapor RE 120 (Buchi, Flawil, Switzerland) with reducing the pressure stepwise down to 30 mbar with a diaphragm pump.

The preparation of lipid nanocapsules (LNC) was based on a phase inversion method[6]. Briefly, an ibuprofen amount equivalent to 2% (w/w) was dissolved in the internal oily triglyceride phase medium-chain triglyceride (18%, w/w) before all preparation steps by magnetic stirring for 5 minutes. The oil phase was then mixed with Solutol HS15 (20%, w/w). Distilled water (60%), sodium chloride (100 mg), and Soybean lecithin (100 mg) were also added to form a total weight of 5 g. Three heating–cooling cycles were performed before adding 5 mL of distilled water at 4°C. The nanocapsules were then stirred for 10 minutes before further analysis.

For testing the permeability of dialysis membrane to the drug ibuprofen, drug solution was prepared in the concentration of 1% in phosphate buffer pH 7.4 and tested for its drug release before testing all types of nanoparticles.

Measurement of the particle size

The prepared particles were analyzed for their particle size and size distribution in terms of the average volume diameters and polydispersity index by photon correlation spectroscopy using particle size analyzer (Brookhaven Instruments Corporation, Holtsville, NY, USA) at fixed angle of 90° at 25°C. The nanoparticles suspension was diluted with distilled water before analysis and samples were analyzed in triplicate.

Determination of in vitro drug release kinetics

Glass basket dialysis method

The study was carried out using a modified USP dissolution apparatus I (Figure 1). Samples, each of 2 mL of the preparation, were placed on a dialysis membrane previously soaked overnight in the release medium. The dialysis membrane was attached to the lower end of a glass tube of 2.2 cm internal diameter and 3.5 cm length replacing the original basket; the total surface area available for drug release was 3.8 cm^2. The tubes were tied up with a rubber to prevent leakage and attached to the apparatus shaft. After fixation to the apparatus, the tubes were immersed in the dissolution vessel that contained 100 mL of the release medium (Sorenson phosphate buffer pH 7.4) and maintained at 37 ± 0.5°C. Sink conditions were ensured throughout the experiments because the aqueous solubility of ibuprofen as a weak acidic drug is pH dependent and it is freely soluble at pH 7.4. The saturation solubility of ibuprofen in phosphate buffer pH 7.4 as determined experimentally at 37°C was 14.69 g/L. The shafts were then positioned so as to keep the baskets equally dipped in the dissolution medium to a depth of 3 mm. For all experiments, regenerated cellulose dialysis membrane of MWCO 12–14 KDa has been used except for the experiment dealing with the effect of MWCO on drug release, where two alternative cut-offs of 15–25 and 50 KDa were used. The glass baskets were rotated at 50 rpm and aliquots from the release medium were assayed spectrophotometrically at predetermined time points using online connected UV spectrophotometer. The samples were assayed at 264 nm for ibuprofen content and the concentration of the drug was determined from the previously constructed calibration curve. The presence of other formulation ingredients did not interfere with the analysis as confirmed from control experiments. Results were averaged for six experiments and were expressed as percentage of theoretical drug load.

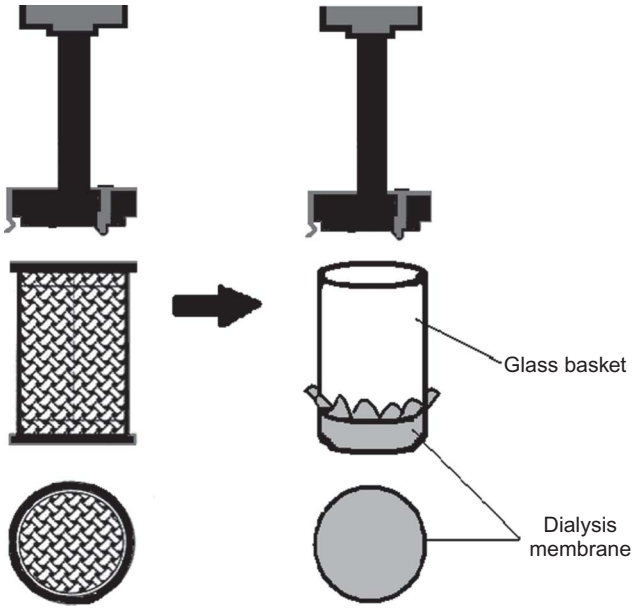

Figure 1. Design of the glass baskets (right) compared to conventional baskets (left).

Dialysis bags method

In vitro drug release from the different colloidal carriers was tested with dialysis technique. Dialysis bags of regenerated cellulose dialysis membrane of MWCO 12–14 KDa (surface area of 25.12 cm^2) were soaked in the release medium overnight and then 2 mL of the preparations were placed in each dialysis bag and sealed in both ends with clips. Bags are immersed in 100 mL of the dissolution medium and kept at 37°C in a shaking water bath moving at a speed of 50 rpm. Aliquots of 2 mL were withdrawn from the dissolution medium at predetermined time intervals and assayed spectrophotometrically for the drug content. Six experiments were performed and average results were obtained.

Results

The principal particle properties, such as particle size and polydispersity, of the different model colloidal carriers used in this study are given in Table 1. They were all in the nanometer range with low polydispersity indicating the homogeneity of the particle size.

Dialysis bag and the new method (GBD) showed similar permeability for ibuprofen solution varying of t50%, respectively, from 0.5 to 1 hour.

First evaluations of the glass baskets method have been done by performing release experiment for the LNC in different volumes of dissolution medium (50, 100, and 200 mL). Results revealed faster drug release rate in case of using 200 mL, whereas the 50 and 100 mL had no significant difference, with releasing 96% and 99% of the drug, respectively, after 24 hours, although in all cases sink conditions were met (Figure 2a). Different rotation speeds (50, 75, and 100 rpm) have been also

Table 1. Particle size analyses of the different types of colloidal systems.

Formula code	Particle size (nm)	Polydispersity index (PI)
LNC	44.0 ± 0.8	0.041 ± 0.004
NP100	123.6 ± 11.3	0.005 ± 0.000
NP300	310.2 ± 23.8	0.012 ± 0.006
NP600	608.5 ± 29.1	0.070 ± 0.003
Liposomes	113.0 ± 12.8	0.143 ± 0.020

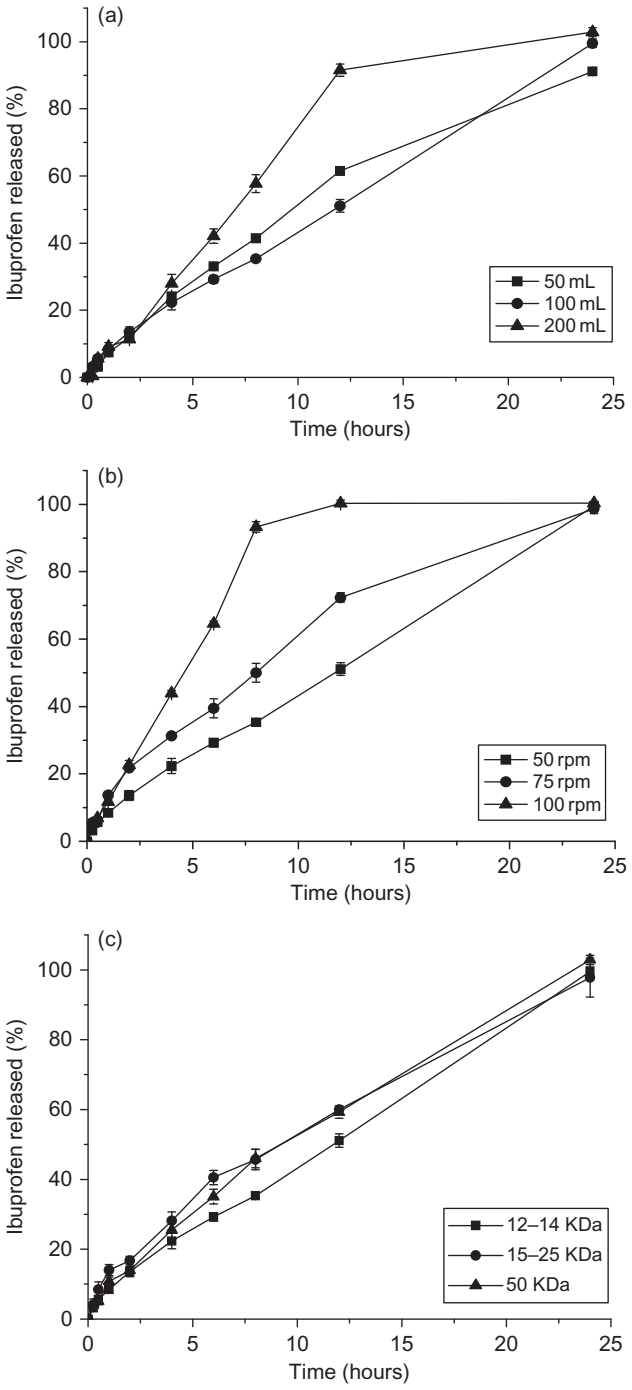

Figure 2. In vitro drug release from LNC using glass baskets in the dissolution tester, with dialysis area of 3.8 cm^2 at 37°C (n = 6). (a) Using different volumes of release medium (phosphate buffer pH 7.4) at 50 rpm and dialysis membrane MWCO 12–14 KDa. (b) Using different rotation speeds in 100 mL phosphate buffer pH 7.4 and dialysis membrane MWCO 12–14 KDa. (c) Using different dialysis membrane pore sizes in 100 mL phosphate buffer pH 7.4 at 50 rpm.

used during the drug release testing of LNC. Increasing the speed has significantly increased the drug release rate (Figure 2b).

In order to study the effect of dialysis membrane pore size, drug release testing was done using regenerated cellulose dialysis membranes of molecular weight cut-off of 12–14, 15–25, and 50 KDa. Only a very slight increase of drug release rate was observed upon increasing the membrane pore size (Figure 2c).

The reproducibility of the GBD was evaluated by using the coefficient of variation between the replicates of LNC drug release results. The data in Figure 3 and Table 2 indicate the high reproducibility of results.

Subsequently, the three different types of colloidal carriers have been compared in terms of their drug release profiles using both the GBD and the standard dialysis bag methods. The results shown in Figure 4a indicate that the dialysis bags method produced very similar release profiles for the three colloidal systems, LNC, polymeric nanoparticles 300 nm, and liposomes. A similar observation was obtained upon comparing the polymeric nanoparticles of different sizes 100, 300, and 600 nm (Figure 4b). In vitro drug release of the polymer nanoparticles of different sizes using the dialysis bags yielded overlapping dissolution profiles and no significant difference could be detected between them. The same formulations tested with the GBD method led to

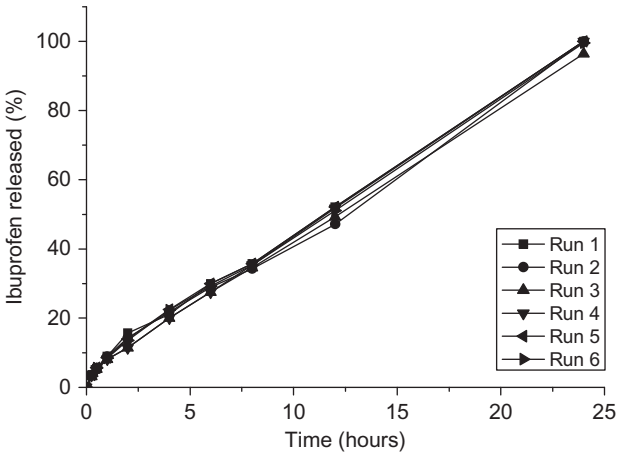

Figure 3. In vitro drug release from LNC using glass baskets in the dissolution tester at 37°C and 50 rpm in 100 mL phosphate buffer pH 7.4 using dialysis membrane MWCO 12–14 KDa (n = 6) showing the low standard deviation between the six replicates.

Table 2. Coefficient of variation for the drug release from LNC using GBD method.

Time (hours)	Coefficient of variation (%)
0.25	3.6
0.50	3.4
1	2.2
2	2.1
4	1.9
6	0.77
8	1.6
12	0.73
24	1.3

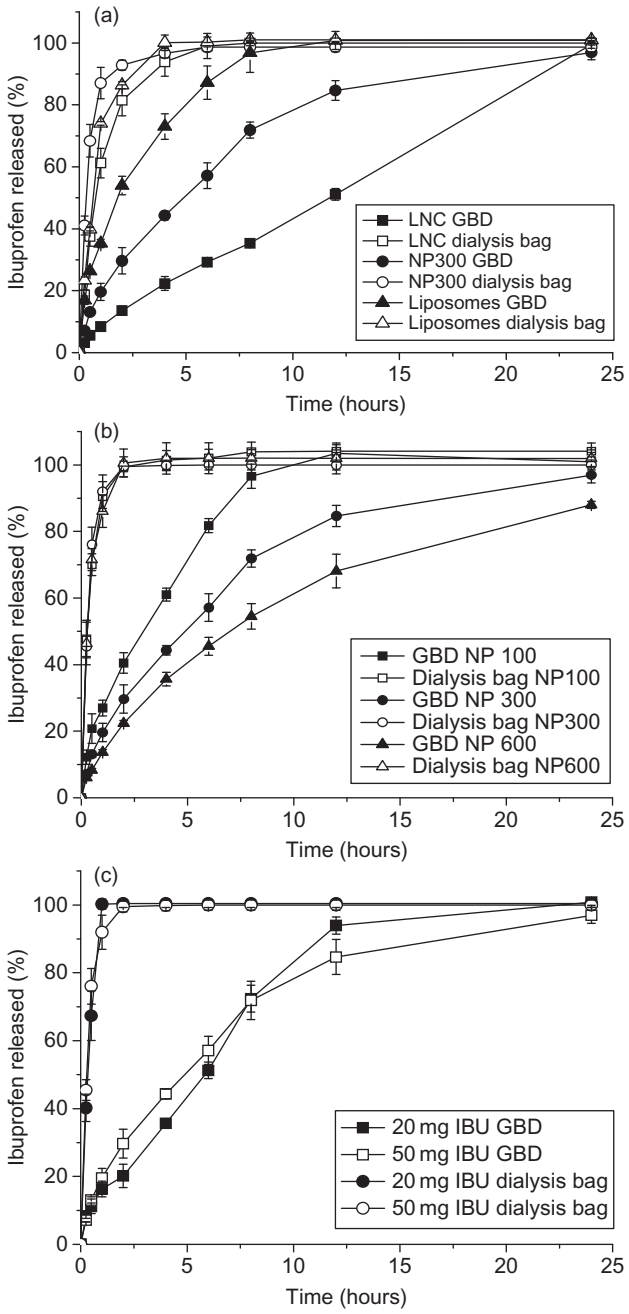

Figure 4. In vitro drug release using dialysis bags (SA: 25.12 cm^2) and glass baskets in the dissolution tester (SA: 3.8 cm^2) at 37°C and 50 rpm in 100 mL phosphate buffer pH 7.4 ($n = 6$), MWCO 12–14 KDa. (a) From different types of nanocarriers: LNC, polymer NP, and liposomes. (b) From different particle sizes of polymer nanoparticles. (c) From polymer nanoparticles (300 nm) containing different drug loadings.

significantly decreased drug release rate when the particle size increased.

Although the results were comparable in case of polymeric NP300 loaded with different amounts of ibuprofen within each method (Figure 4c), data from the GBD underlined a higher discriminating power of this latter method.

Discussion

An important aspect in the evaluation of drug delivery systems is the rate at which the drug is released from the carrier. In vitro drug release tests are generally used not only in the quality control of drug formulation, but also to predict in vivo behavior and to study the structure of the dissolving carrier[14]. In case of colloidal drug delivery systems, the evaluation of in vitro drug release is not an easy task. This is because of the difficulty of separating the released drug from the drug still bound to the very small carrier.

The method described here is a membrane diffusion method developed as a modification to the basket system used in drug release of solid dosage forms using a USP dissolution tester. Similar diffusion-bag-related methods have been described in the context of conventional dosage forms[15–17], whereas the method described here has been adjusted for the testing of colloidal drug delivery systems. The method offers a constant surface area for drug release compared to the dialysis bag method allowing for better reproducibility of the results. It has also the advantage of being simple, cheap, and easy to be carried out in any pharmaceutical laboratory. The use of dissolution tester with online connected UV spectrophotometer allows the frequent sampling, especially in the first hour of drug release. Therefore, this method would be useful for the fast-releasing formulations. It can be used for all types of drugs as long as the drug can permeate through the membrane and an appropriate analytical method exists. It also proved to be suitable for the comparison purposes between different formulations and studying the effect of various formulation parameters.

The dissolution volume has an impact on the drug release rate where it was found that increasing the dissolution volume has two opposing effects. The first is in the direction of increasing the drug release rate by increasing the concentration driving force. Although lower dissolution volumes of the acceptor phase could be interesting for analytical purposes, it should be kept in mind that the lower the volume, the higher the fluid flow rate, and the receptor solution velocities increase considerably leading to higher release rates at any given rpm[18]. Therefore, it is essential to keep the dissolution volume constant throughout the development of an effective and reproducible drug release experiment.

The different rotation speeds had also a prominent effect on the rate of drug release from LNC where the higher the rpm used, the faster the drug releases. This is because of the increased turbulence or agitation in the dissolution medium caused by the higher rotation speed by the glass baskets which in turn can lead to faster diffusion of the drug to the release medium[19–21]. The agitation speed and pattern of the glass baskets can be easily standardized and fixed compared to the case of dialysis bags. The agitation in dialysis bags is sometimes

provided by magnetic stirrers or shaking water baths where the kinetics of stirring will be hardly comparable.

It was important to test the effect of dialysis membrane molecular weight cut-off range on the rate of drug release as it has been previously recommended to use the highest ranges to minimize the membrane retarding effect on drug release[1,9]. Surprisingly, we did not find any significant differences between the three tested types of membranes. This may be because the molecular weight of the drug ibuprofen was much smaller than all the used pore sizes.

We found that the dialysis bag method can hardly provide discriminating results for different types of nano-sized carriers. By this method, liposomes, LNC, and polymeric nanoparticles nearly have the same dissolution profiles and the method can be considered as insufficiently adapted. In case of the GBD method, drug release was relatively slowed down allowing for obtaining discriminating results between the different types of carriers. This might be caused by the relatively smaller release area compared to dialysis bags. Indeed, ibuprofen generally provides relatively fast release at pH 7.4 because of its high solubility at that pH. The fastest drug release was obtained from liposomes, which can be explained by the rapid leakage of the drug entrapped in the lipid bilayer of liposomal surface. The release rate was also fastened because of the small size of liposomes, the smaller the size, the greater the curvature of the liposomes surface and the easier the escape of the drug compared to the larger sizes[22].

The comparison between the polymeric nanoparticles and the LNC has revealed that drug release was faster from the polymeric NPs compared to the LNC. Release profile from the polymeric NP seems to be mainly controlled by the diffusion of the drug through the polymer matrix as it has been previously reported[23] with an initial burst release that is always explained by the amount of the drug adsorbed on particle surface. The slowest release rate obtained from the LNC is probably because of the slow diffusion of the drug from the oily core of the capsule to the aqueous medium because of the greater interaction between drug and the lipid oil core.

Regarding the effect of particle size on the in vitro drug release, different sizes of the polymeric nanoparticles were tested. Increasing the particle size has decreased the release rate significantly because of the decreased surface area of the particles leading to lower diffusion rates of the drug. Differences were clearly visible with the GBD method, whereas dialysis bags could not differentiate between the different formulations.

With polymeric nanoparticles of similar size but using two different drug loads, 20 and 50 mg ibuprofen, similar release profiles were obtained. It has been reported that drug loading had no effect on the particle size of the carrier system[24]. This similarity in particle size might explain the comparable drug release behavior in both cases.

Generally, comparing GBD method with the standard dialysis bag method showed that the GBD method is much more discriminating and can provide an excellent tool for the assessment of manufacturing methods and formulation factors on drug release from these carrier systems. It can be also used as a good quality control tool because of the high reproducibility of its results. This reproducibility was clear from the low standard deviation between the six replicates of each experiment. One formula (LNC) was taken as an example and the variation coefficient was calculated for the six readings at each time point. The low coefficient of variation could prove the reproducibility of the method. The coefficient of variation (CV) was relatively higher in the early time points because of the small values of percent drug released at these points so even very small standard deviations would give a high value of variation coefficient.

Although the partitioning between in and outside of the glass basket, triggered by the dialysis membrane, may have a distinct influence on the release kinetics, this should be considered as an acceptable inconveniency of the presented method. On the other side, it allows for a standardized analysis of drug release from colloidal drug delivery systems which was not yet obtained with other approaches.

The method should mainly be considered as a tool for quality control uniformizing dialysis bag experiments. This approach has not so much the intention to mimic in vivo conditions, as does not the dialysis bag method either, but provides a tool for identification of differences in release kinetics from colloidal carriers not detectable with the 'traditional' methods.

Conclusion

The glass basket method appears to be very sensitive, reproducible, and easy method that can be used for analyzing the drug release from different types of colloidal drug delivery systems. It can discriminate differences between different formulations and types of carriers, which are hardly detectable with the existing methods. The potential of this method is not so much to describe in vivo conditions, but to elucidate differences in physicochemical properties between different systems which remained undetected with previously applied techniques.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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