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Design and evaluation of an early stage drug release apparatus

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Abstract

This paper describes the design and evaluation of an early stage drug release apparatus (ERA) to determine drug release from pellets at times less than 1 min. The apparatus comprises a stirred sample chamber in which the sample is retained by a BS150 mesh screen (0.106 mm), and a series of jacketed cups containing the medium (80 ml) which are raised and lowered in turn over the fixed sample chamber for specified periods. Three types of early release studies were used: single 60 s study (single cup), 10 s followed by 50 s (two cups) and 10, 20, 30 ... 60 s multiple changeover differential release (six cups). The effects of stirrer speed, stirrer position and multiple changeover on drug release from standard paracetamol-alginate pellets were investigated. Drug release rates from non-disintegrating pellets were reproducibly determined. The three types of early release study schemes yielded reproducible drug release data over sampling times less than 1 min. Stirrer speed, and depth, and changeover motion of release cups affected drug release but yielded reproducible results. Release from the standard pellets used to study the apparatus took 3 days to stabilize and remained stable thereafter. The apparatus can be used for screening of pellet formulations of sparingly soluble drugs during their developmental stage and regular quality assurance studies of pellets (>150 mesh size). Along with early release studies of pellets, it could be easily modified to study other types of formulations and for automation.

Keywords: Early stage drug release; Burst release; Release apparatus

1. Introduction

The study of drug release from dosage forms at early times after wetting is important for taste-masking and to understand drug embedding and release processes. Early stage release is important when screening for organoleptic purposes because a non-palatable drug formulation may be accepted or rejected by the exteroceptive sense of taste during its short residence in the mouth. This depends on the specific drug and the supra-threshold amount released in the mouth (Best and Taylor, 1990). Typical residence times in the mouth of 30 s have been reported (Taylor, 1996). The complex aspect of taste (Best and Taylor, 1990; Guyton and Hall, 2000) and the other factors responsible for non-palatability, other than the drug concentration, have been discussed elsewhere (Taylor, 1996; Lawless and Heymann, 1998). For drug embeddings, factors which improve the extent of embedding of the drug particles into a polymer matrix may be investigated using early stage drug release to study burst release and the subsequent drug release over the first 2 min.

Although sensory screening panels can be used to evaluate products, this approach is expensive and therefore it would be preferable to avoid it at early

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stages of formulation development. Moreover, the sensory study only gives a relative rating against time (Lawless and Heymann, 1998) and it does not give the formulation scientist quantitative data of the amount of drug released from the formulation during the early stages. Consequently a method to study early stage drug release would be of value.

Various types of dissolution apparatus have been reported for determining in vitro drug release for different purposes (Abdou, 1989; Banakar, 1992). Very few deal specifically with determination of early stage drug release.

The most common among the apparatuses is the beaker type apparatus. Drug release profiles in the first 30 min using USP dissolution apparatus type 2 have been used to screen formulations (Ng, 1993); however, this time frame does not account for the early stage drug release. The paddle bead, a modified beaker method, originally developed for the purpose of simulating gastric movements (Aoki et al., 1993) was used to simulate the chewing action on drug release (Hanawa et al., 1995). More recently, absence of drug release from tablets during the first minute was studied using a beaker type apparatus (Kaneko et al., 1997). This apparatus has the problem that the time frame is relatively long (1 min) and the drug releasing chamber is large. Small samples withdrawn from the large volume at early times may not be representative due to inadequate mixing.

The problems associated with other official apparatuses are as follows. In case of USP type 3 apparatus, complete withdrawal of media is possible but the shortest time is 1 min. A flowthrough cell has also been used to determine drug release from pellets intended for bitter taste masking (Sjoequist et al., 1985). Typical flow rates of 4–16 ml/min have been recommended (USP, 2003). Higher uniform flow rates, required for burst release determination, are limited by pump restrictions and back pressure.

Other improvised methods to study drug release have been reported. A drug release apparatus using a low volume of release medium for non-disintegrating pellets and granules, has been attempted using a rotating bottle apparatus (Ramsey et al., 1980). However, this apparatus may not be reproducible for very short times. An injection syringe has also been used to determine drug release from granules by agitating the syringe in a controlled way (revolved five times in 30 s) before analysis (Shirai et al., 1993). A drug release apparatus, consisting of several release cups, has been reported in Chemical Abstracts as patents (Ersue and Neddermeyer, 1995). It is an automated beaker type dissolution apparatus not intended for early stage drug release. A minibasket with a covering lid has been used to transfer pellets from a paddle type apparatus to a flow through cell to determine drug release from pellets in different media/apparatus (Loos et al., 2000). This method is primarily suited for determination of drug release from enteric coated solid dosage forms using official USP methods, for example, Paddle type (type 2) combined with flow through apparatus.

This paper describes the design and validation of an early release apparatus. The utility of the apparatus to distinguish the behaviors of different formulations is demonstrated using novel paracetamol granule formulations. Also different time schemes to study early stage (first minute) drug release are reported for the above non-disintegrating granules.

2. Materials and methods

2.1. Materials

Paracetamol was obtained from BDH, Poole, UK, and Keltone HVCR (Alginate, 400 cps, milled fine PS, Medium G) from ISP Alginates, USA. All other materials used were of analytical grade.

2.1.1. Standard embeddings (SE)

A uniform dry mix of paracetamol and Keltone HVCR milled (ratio 1:2; both passed through 100 mesh; 0.106 mm) was granulated in a planetary mixer using water and dried at 55–60 °C for 12–15 h, de-dusted and a size fraction of 0.8–1.0 mm selected. The embeddings were treated in sub-lots with calcium chloride di-hydrate solution (100 mg/ml) at 25 °C for 5 min of which 4 min was under stirring (240 rpm) with 30 s resting time at the beginning and end of the 5 min period, and then filtered through a G1 sintered glass funnel under suction. The treated embedding were dried at 55–60 °C for 12–15 h. The ratio of untreated pellet to treatment solution was kept constant (about 1:10 w/v). Embeddings were stored in a dessicator over silica gel throughout the period of study.

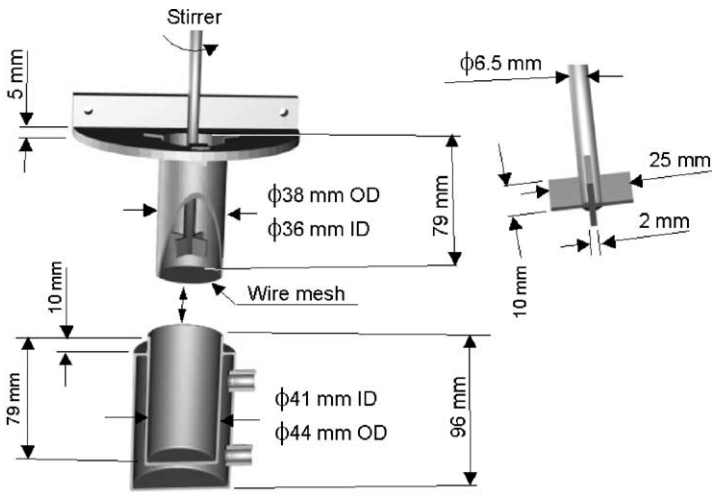

Fig. 1. Front view of essential parts of ERA. Top: sample holder assembly (SH); bottom: a jacketed release cup assembly (RC).

2.1.2. Preparation of formulations

Other embeddings were prepared using drug to alginate ratios of 1:1 (DA 11); 1:2 (DA 12); and 1:3 (DA 13). Dried granules 0.8–1.0 mm size fraction were subdivided into two parts and treated separately with calcium chloride solution for 1 min of which 30 s (4 min for standard embeddings) under stirring at 240 rpm with 15 s resting time at the beginning and end prior to filtration. All other treatment conditions were the same as for standard embeddings.

2.2. In vitro apparatus (ERA)

The early stage drug release apparatus (ERA) consists of a cylindrical sample holder and jacketed stainless steel (SS) cups (Fig. 1).

The sample holder is attached to the stirrer assembly so that the stirrer can enter the open end of the sample holder. The lower end is closed by a SS wire sieve (150 mesh; 0.106 mm) which retains the drug embeddings. The cylindrical jacketed SS cups, containing release medium, were raised by hand over the SH attachment plate of the SH and lowered freely.

2.3. Operation of ERA

Treated paracetamol embeddings (30–40 mg accurately weighed) were placed into the dried sample holder with the stirrer on at a selected speed and position. A thermostated ($25 \pm 0.5\,^{\circ}C$) cup containing 80 ml pre-equilibrated release medium (water) was raised to the sample holder attachment plate so that the embeddings (in the sample holder) were immersed in the medium for a specified time. At the end of the stipulated time the cup was quickly lowered. In the case of more than one sampling, the subsequent cups containing pre-equilibriated media were raised and lowered in turn for specified times. The samples were filtered if necessary prior to dilution with 0.1 M NaOH, and analyzed by a validated UV assay ($\lambda = 257$ nm). Three sampling schemes were studied. *Single sampling*: The sample holder containing particles was immersed once for a period of 60 s. *Double sampling*: The sample was immersed for 10 s (cup 1) and then for 50 s (cup 2). *Multiple sampling*: The sample was immersed for 6×10 s periods using six cups. The maximum time for six samplings was not more than 62 s. The changeover time between cups was less than 2 s and non-cumulative. Raising and lowering of the cups were done manually.

2.4. Effect of stirrer position and stirring speed (rpm) on drug release

The drug release from standard embeddings was studied in triplicate at 0, 50, 100, 150, 200, 240 rpm each at stirrer positions 5 and 45 mm above the wire mesh using the double sampling strategy.

Table 1
Cup movements used to study the effect of cup changeovers on drug release from standard embeddings (series C)

Pellet set	Sampling points						
	0 s	10 s	20 s	30 s	40 s	50 s	60 s
1	↑	↓	–	–	–	–	–
2	↑	↓↑	↓	–	–	–	–
3	↑	↓↑	↓↑	↓	–	–	–
4	↑	↓↑	↓↑	↓↑	↓	–	–
5	↑	↓↑	↓↑	↓↑	↓↑	↓	–
6	↑	↓↑	↓↑	↓↑	↓↑	↓↑	↓

Raising of cups (↑); lowering of cup (↓) lowering followed by raising of cup (mimicking changeover of cups) (↓↑). Time for (↓↑) was about 2 s.

2.5. Effect of changeover during multiple sampling on drug release

To study the effect of multiple raising and lowering of cups three types of sampling were compared.

Series A: The single sampling strategy was used for different time periods 10, 20, 30, 40, 50 s as well as the usual 60 s, using a fresh sample of standard embeddings each time.

Series B: A multiple sampling strategy as described above.

Series C: In order to study the effect of changing the cups on drug release, the changeover action was simulated using a number of strategies (Table 1).

For these studies the stirrer speed, position, medium temperature and volume were held constant at 240 rpm, 5 mm above the wire mesh of the sample holder, 25 °C and 80 ml, respectively.

2.6. Data analysis

The results of dissolution studies are expressed as the means of at least three experiments ±S.D. Balanced ANOVA were performed on percent released data using MINITAB Release 12.1 and a level of significance of $P = 0.05$.

3. Results and discussion

3.1. Release from standard embeddings

The variation in release from standard embeddings was determined by performing 10 replicate analyses using the double sampling method. The CVs obtained for 10 s, 50 s and combined (10 and 50 s) intervals were 1.82, 0.93 and 0.77%, respectively. The drug release rate increased over the first 3 days after manufacture but then stabilized (data not shown). In all studies, the release of paracetamol was such that sink conditions (≪10% saturation) were maintained throughout.

3.2. Effect of stirrer position and speed

The amount of drug released in 10 s at 100 and 150 rpm stirrer position 5 mm above wire mesh were significantly higher than those at the corresponding speeds and stirrer position 45 mm above the wire mesh (Fig. 2a). The lower stirrer position (5 mm) subjected the embeddings to increased agitation as the embeddings were near the stirrer blade due to gravity whereas at the higher stirrer position this was not observed as the embeddings were settled on the wire mesh. At 240 rpm such localized agitation of granules was not observed. Below 50 rpm the agitation was too low to

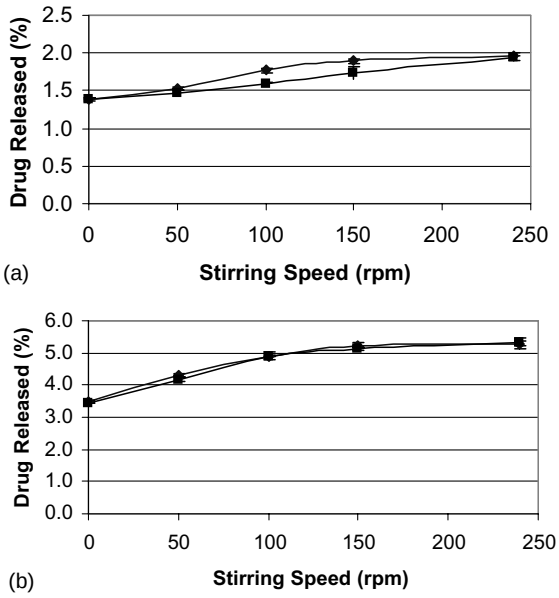

Fig. 2. Effect of stirrer depth (◆) 5 mm, (■) 45 mm and speed on early stage drug release from standard embeddings (a) during the first 10 s and (b) during the subsequent 50 s using the double sampling strategy. Data are means ($n = 3$). Error bars (S.D.) contained with symbols.

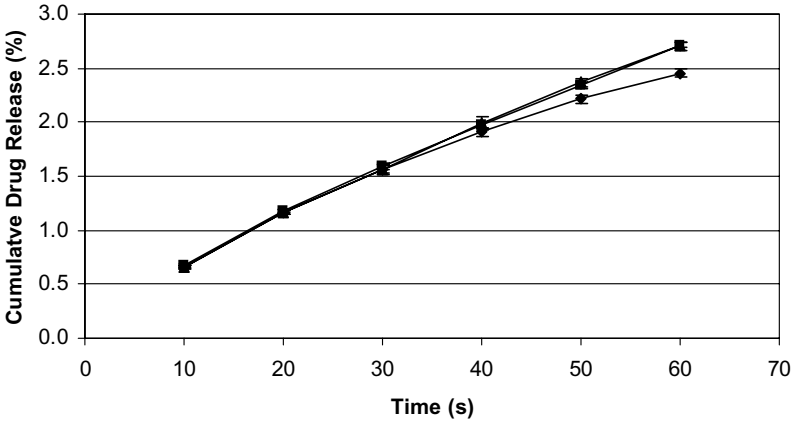

Fig. 3. Effect of change over motion on early stage cumulative drug release from standard embeddings during multiple change over study (total time 60 s). Drug release from standard embeddings: series A (◆): embeddings not subjected to change over motion (single sampling); series B (■): embeddings subjected to multiple sampling scheme using 6 × 10 s; series C (▲): embeddings subjected to change over mimicking action using single cup (Table 1). Data are means ($n = 3$). Error bars (S.D.) contained with symbols.

cause a difference. However, no significant difference was observed in the case of 50 s data for all the speeds studied suggesting the drug release becomes less sensitive to agitation during the second sampling stage (Fig. 2a and b).

These data indicate it is better to keep the stirrer at 5 mm to study agitation sensitive granules; however, adjusting the stirrer blade closer to the wire mesh is not advisable as it might damage the granules (especially during cup changeover).

3.3. Effect of changeover motion during multiple sampling

The effect of change over motion on early stage release from standard embeddings was small and reproducible (Fig. 3). Until the fourth sampling (40 s) the amount of drug released from the embeddings not subjected to cup changeover (series A) did not differ from the embeddings subjected to changeover (series B and C). From 50 s onwards the amount released from the embeddings (series B and C) was significantly higher than from granules not subjected to such motion (series A) (Fig. 3). For longer study periods or an increased number of changeovers, consideration may be required with this type of granule system. Pellets containing a more soluble drug could be more sensitive to the effect of changeover motion.

3.4. Study of formulations

Three formulations with different drug to excipient ratios were studied using the three sampling schemes.

The drug release using the single sampling strategy differed significantly from formulation to formulation but not from batch to batch (Fig. 4). Also the amount of drug released in 10 and 50 s using the double sampling strategy differed significantly from formulation to formulation but not between batches of formulations (Fig. 5).

Typical early release data for batches DA 11, DA 12, DA 13 and SE using the multiple sampling strategy are presented in Fig. 6. The peak at the beginning of the release curves (0–10 s) showed the burst release followed by steady decrease and stabilization of drug release. As the proportion of the polymer increased there was a reduction in the release rate (Fig. 6). The increased amount of early stage drug release (both burst effect and subsequent drug release) of Batch No. DA 12 over SE (both having the same initial drug to polymer ratio 1:2) demonstrates the effect of the treatment process. The longer stirring time during preparation (4 min for SE compared to 30 s for DA 12) probably removed more drug from the pellet surface causing the lower drug release.

Data from Fig. 6 are represented as cumulative drug release in Fig. 7. This form of presentation obscures the processes involved in the early release.

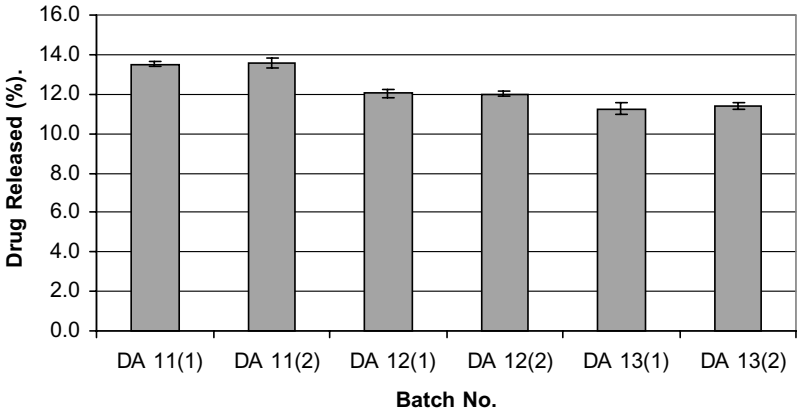

Fig. 4. Early stage drug release (total time 60 s) from three formulations (duplicate batches) using the single sampling strategy. Data are means ± S.D. ($n = 3$).

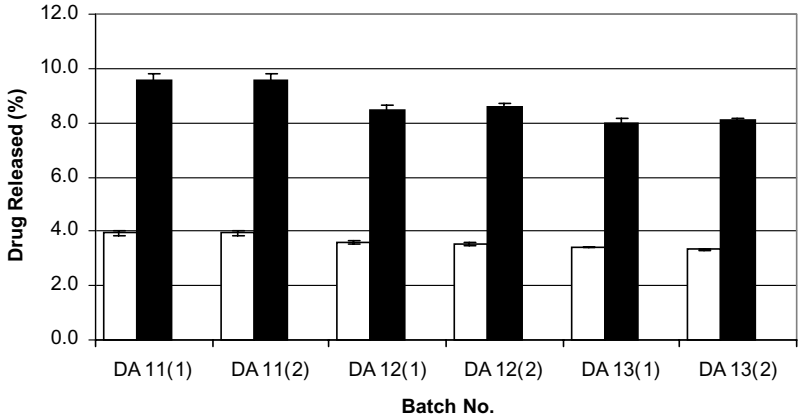

Fig. 5. Early stage drug release from three formulations (duplicate batches) using the double sampling strategy 10 s (□), 50 s (■). Data are means ± S.D. ($n = 3$).

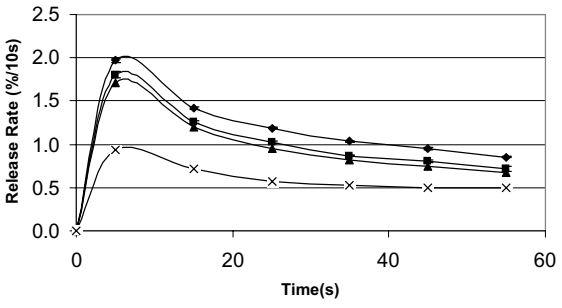

Fig. 6. Drug released in 10 s periods from four different formulation using the multiple sampling strategy. DA 11: (◆); DA 12: (■); DA 13: (▲) and SE: (×). Data are means ($n = 3$). Error bars (S.D.) contained with symbols.

To ensure that the release data were not affected by drug dissolution limitations at the short time intervals studied, a higher mass of embeddings from the same batch (80 mg instead of about 34 mg drug containing pellets) was studied. The extrapolated results (80–34 mg) were found to be not significantly different.

All the experiments in this study were conducted at 25 °C. However, studies could be conducted at other temperatures (e.g. 37 °C) since the sample cups are thermostated. From a taste masking perspective, 25 °C could be seen as a compromise between mouth and ambient temperatures; so early drug release in the mouth could occur at about 25 °C, but this remains to be confirmed.

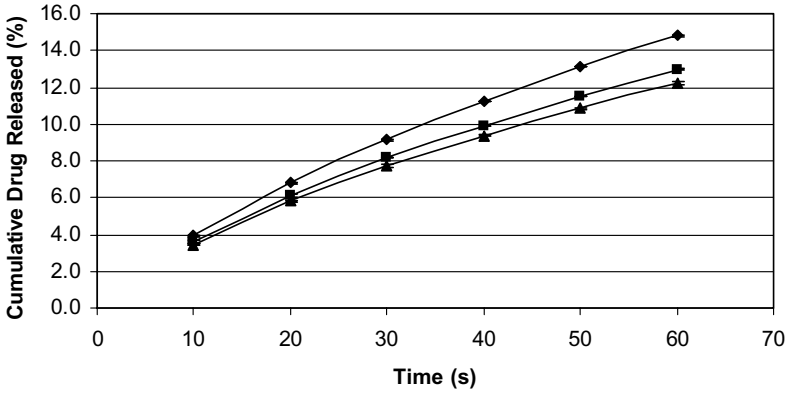

Fig. 7. Early stage cumulative drug release from three types of formulations using the multiple sampling strategy. DA 11: (◆); DA 12: (■); and DA 13: (▲). Data are means ($n = 3$). Error bars (S.D.) contained with symbols.

4. Conclusion

A simple apparatus was designed for measuring early stage drug release from pellets and granules having size larger than 150 BS-410 (0.106 mm). With little modification it could be used to study early stage drug release from other formulations containing drugs of different solubilities in tablets, films, gel forming particles. To study drug release from particles less than 150 mesh a possible way would be to fix the particles (Goldberg et al., 1965) onto the inner wall of the sample holder by a suitable adhesive prior to sampling. This apparatus has application in taste masking research allowing drug release to be studied in the time periods dosage forms are likely to spend in the mouth. Further, knowledge of early stage release is useful in understanding embedding and release processes. Due to complete withdrawal of release medium the sample is representative even at short time intervals. The agitation level can be varied by altering the stirrer speed. To simulate chewing action in the mouth and intestinal movements, polystyrene beads might be incorporated in the apparatus with minor modifications of the sample holder. The apparatus could be easily automated and used to study formulations during the developmental stage and for routine quality assurance work.

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