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ORAL HYDROPHILIC MATRICES HAVING NON UNIFORM DRUG DISTRIBUTION FOR ZERO-ORDER RELEASE: A LITERATURE REVIEW

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KEYWORDS

Matrix systems, hydrophilic polymer, oral prolonged release, zero-order release, non-uniform drug distribution, gradient drug concentration

ABSTRACT

Oral hydrophilic matrices for prolonged release mostly show a decrease in the rate of drug release over time, owing to the increasing length of the diffusional path and progressive reduction of the area at the interface between glassy and rubbery matrix. In addition, burst effect may also occur due to the fraction of drug present on the surface of the system, which is released when the external polymer particles are not fully swollen yet. Different strategies have been attempted in order to address these issues and, ideally, to reach zero-order release. The approaches proposed are based on geometric modulation of the release area, control of the swelling behavior or initial non-uniform distribution of the active ingredient throughout the polymer matrix. The present article offers an extensive analysis of the various methods described in the literature for reaching zero-order release leveraging non-uniform distribution of the drug in hydrophilic polymeric systems. In this respect, special attention is given to the design of the main delivery platforms reviewed, their manufacturing, *in vitro* release profiles and analytical techniques for assessing drug concentration patterns within the solid units.

1. Introduction

Despite the presence in the literature of more innovative dosage forms for obtaining oral prolonged release of drugs, matrices prepared by tableting are nowadays the most widespread system thanks to the flexibility they guarantee in the release modulation and to the low production costs [1–4]. Among these, hydrophilic matrix tablets have long been the most frequently used formulations intended for such an application [5–7]. Typically, hydrophilic matrices can easily be obtained by direct compression of a powder mixture of drugs with swellable polymers and other additives, e.g. fillers and lubricants, to aid processing. Particularly, hydrophilic cellulose derivatives are commonly employed because of the advantages they offer, mainly including their status of generally regarded as safe (GRAS) materials and availability in several grades allowing flexibility of performance [1,4,8].

When hydrophilic matrices come into contact with water, a structural change occurs: the polymer turns from the glassy to the rubbery state, which is associated with a swelling phenomenon. Once the glass transition temperature (Tg) is reached, the polymer chains start to relax and eventually disentangle. According to the physico-chemical characteristics of the polymer (type, molecular weight and degree of substitution), the volume of the system can increase as the solvent/polymer interaction progresses [6,9]. The swelling and the continuous inward flux of liquid break intra- and inter-molecular hydrogen bonds or mechanical links formed during compaction [10]. The highly swollen outer region has the highest amount of water, and the gel that is formed may become mechanically weak thus being susceptible to surface dissolution and erosion. Provided that the amount of polymer is sufficiently high (20-30%), the resulting gel layer prevents disintegration of the system [1,11,12]. To comprehensively describe this process, the geometry of the matrix is important. In the case of cylinders, both axial and radial mass transport can take place [13,14]. The innermost region of the matrix system remains essentially dry and holds its glassy state for a longer period of time [6,15]. While diffusion is negligible in the dry matrix, drug molecules can more easily diffuse in the swollen

portion of the system and be released [16]. The drug mass transport can either be driven by the concentration gradient (Fickian diffusion) or governed by the polymer swelling (Case-II transport). When the rates of these two phenomena turn out comparable, the diffusional release is referred to as anomalous (non-Fickian) transport [17–21]. If the initial concentration of the drug in the system is much higher than its solubility, a region is also present where the drug is still undissolved and suspended in the fully swollen polymer. Fig. 1 reports a comprehensive representation of all possible changes occurring upon interaction with the aqueous medium of a hydrophilic matrix prepared by tableting a binary mixture of polymer and drug, with drug loading per unit volume being higher than the drug solubility. Three morphologically and structurally different zones separated by sharp boundaries named "fronts", at which a sudden change in the physical state of the polymer and/or the drug can be observed, are identified [5,22]:

• a glassy portion of matrix, not yet reached by the solvent, with solid polymer and solid drug, externally delimited by the *swelling front* (*S-S'*);

• a portion of the matrix in which undissolved drug particles are suspended in the swollen polymer and dissolved drug has a concentration equal to solubility (C_s). This portion is delimited externally by the *diffusion front* (*D-D'*). The thickness of such a portion increases when a poorly soluble drug is concerned;

• an external gel layer, where the drug is dissolved and polymer chains undergo dissolution and/or erosion phenomena, delimited externally by the *erosion front* (*E-E'*).

Particularly, the figure refers to the most common case of a high molecular weight polymer (i.e. HPMC type 2208, 4.000 cps), where, in the time frame of release, the erosion front is found to be positioned externally with respect to the initial surface (*I-I'*) following expansion of the matrix at defined hydrodynamic conditions. Otherwise, if lower molecular weight polymers are used, dissolution/erosion could result in positioning of the erosion front internally with respect to the initial surface of the system.
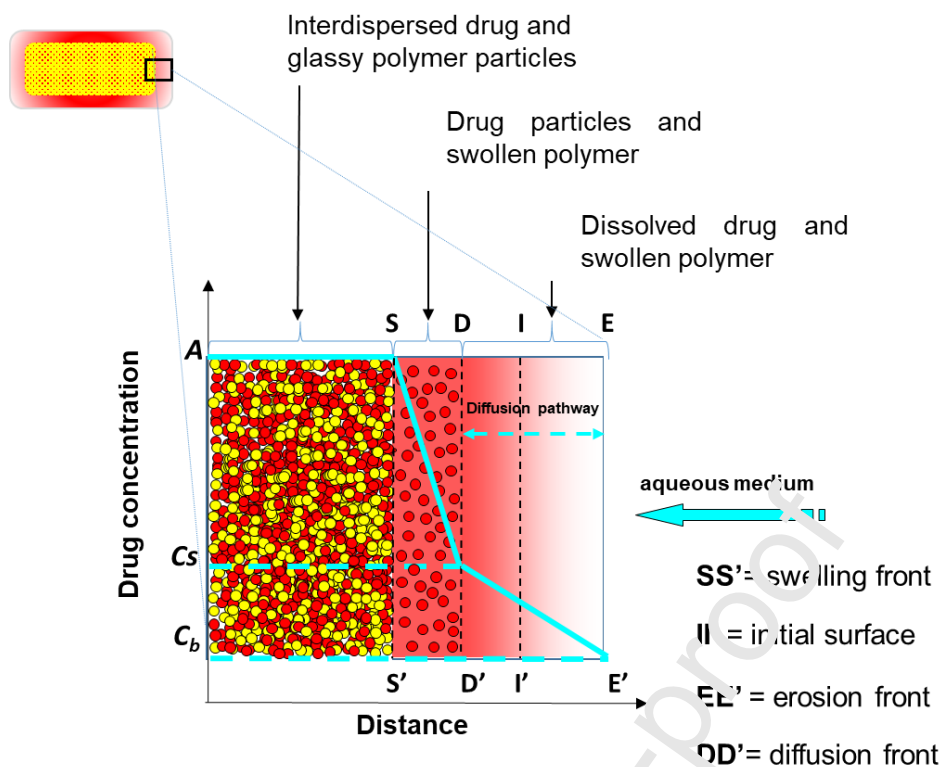
Fig. 1. Comprehensive schematic of possible modifications occurring upon interaction of a drug-containing hydrophilic matrix with aqueous medium. Drug concentration and diffusion distance are represented on arbitrary scales. Swelling, erosion and diffusion fronts along with the initial surface are marked. Drug loading (A), solubility (Cs) and external bulk concentration (Cb) are expressed per unit volume.

The release rate of the drug is also linked to its solubility: highly soluble drugs can render gel structure more porous and determine faster drug release. Moreover, this may establish a steep concentration gradient between the internal and external microenvironments, driving outward diffusion of drug molecules in solution. On the other hand, the release of poorly soluble drugs, which mainly occurs by erosion of the gel matrix, can be quite slow [23,24].

When the matrix first comes into contact with an aqueous fluid, the drug particles that are on its surface tend to dissolve before the outer polymer is fully swollen and the release-controlling mechanism is operating, causing an initial higher rate of release[25]. This phenomenon, described as "burst effect", happens in a relatively short time compared to the overall duration of release. Even if in some sporadic situations the burst effect can be favorable, in most cases it is considered as a negative result. After the burst, the release profile tends to linearity and subsequently the release rate decreases over time.

The release kinetics is related to the rate of diffusion of the drug in the gel and the rate of polymer/solvent interaction (swelling front movement). This can overall be described by the following equation [6]:

$$\frac{M_t}{M_\infty} = k \cdot t^n \qquad (1)$$

Mt/M_∞ is the fraction of drug released at time t, diffusional exponent n indicates the mechanism/kinetics of release and k is a constant incorporating structural and geometrical characteristics of the matrix. In the case of slabs/planar units, n=0.5 refers to Fickian diffusion, n=1.0 to Case-II transport and $0.5<n<1.0$ to anomalous (non-Fickian) transport. Analysis of data is usually performed in the portion of the curve where the fraction of drug released, $\frac{M_t}{M_\infty}$, is < 0.60 [6,26,27]. For enabling correct interpretation of release mechanisms, good reproducibility of data is required and statistical analysis needs to be performed using 95% confidence limits [26,28].

Eq. (1) can also be used for merely descriptive purposes to analyze drug release results from delivery systems in order to assess whether the release is of zero order (n=1) or approaching that (n→1). For instance, this may apply to cases where dissolution/erosion of the swollen matrix is to be accounted for, possibly leading to constant thickness of the gel layer following synchronization of the swelling and erosion front movements, when the exposed area remains constant. The rate of release is in practice a complex function of solvent/polymer interaction, changes in size and geometry of the tableted matrix and hydrodynamics.

A pioneering example of system intended for zero-order release based on control of the releasing area was designed as a hemispherical monolithic matrix prepared by heating and pressing of drug and polyethylene or ethylene–vinyl acetate copolymer in a brass mold [29]. The system was partially coated by casting with an impermeable film thus exposing to fluids only a cavity in the center of its flat face. Linear release kinetics was achieved over periods of days for small and large molecules.

Since then, many research efforts have been dedicated to reach the goal of zero-order release profiles by the use of different strategies, often combined. These may involve application of partial coatings, mechanical restriction of swelling, design of specific geometries, time-dependent porosity changes and combination of co-extruded layers having different concentration [11,21,30–37]. Proprietary technologies developed include, among others, Geomatrix®, Smatrix™, Procise™, core-in-cup, donut-shaped, RingCap and Dome Matrix® systems [37–43].

Besides through geometric modification of the area exposed to the aqueous fluid, zero-order kinetics can be obtained by employing systems that exhibit a concentration gradient due to non-uniform drug distribution. This strategy is aimed at increasing the concentration of the drug from the outer to the inner parts of the unit to compensate for the reduction of the contact area between the solid drug and the dissolution fluids and for the increasing length of the diffusion pathway. The resulting systems may be manufactured by controlled extraction processes, by applying innovative fabrication methods, such as three-dimensional (3D) printing, electrostatic deposition, controlled sedimentation, multilayer tableting and photo-polymerization, or by more traditional coating and layering techniques.

2. Technologies for non-uniform drug distribution systems

2.1. Controlled drug extraction

The concept and effect of non-uniform initial drug concentration in the dosage form on diffusional release were studied in theory and confirmed *in vitro* [21,44,45]. The non-uniform distribution of the drug throughout the system was obtained by partial desorption of drug from a uniform system through a controlled extraction process. The technique consisted in immersion of the spherical

hydrogel beads in an aqueous environment, which caused incipient swelling and drug depletion starting from the outer portions. Subsequently, the beads were subjected to freeze-drying in order to rapidly remove the solvent and immobilize the sigmoidal distribution of the active ingredient [21,44]. The residual drug in the system was released *in vitro* with kinetics depending on the extraction time (Fig. 2). Starting from an extraction time of 15 min, the release was constant up to approximately 0.60 drug fraction released.
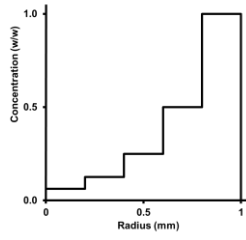

Fig. 2. Effect of controlled-extraction time in water on the in vitro release of oxprenolol hydrochloride. Redrawn from [21,44].

The linear diffusional release could be obtained by a descending sigmoidal-type pattern of initial drug concentration when employing non-eroding spherical systems, as comprehensively reported by Lee (Fig. 3)[5,44,45].With erodible matrices based on hydrophilic polymers, descending staircase-type concentration patterns yielded constant release rate for spherical and cylindrical geometries. The model proposed required to consider the drug to be promptly soluble in contact with water. When loading of the drug in the matrix exceeded its solubility, the effect of initial non-uniform distribution was necessarily related to the movement of the diffusion front. In eroding systems, the diffusional contribution also needed to be taken into account, which could result in an intermediate behavior between that of diffusion- and surface erosion-controlled systems. For example, in the case of the discontinuous descending staircase concentration pattern, the occurrence of diffusion tended to flatten the drug distribution at initial release phases and thereby provide a prolonged constant-rate release[21,45].
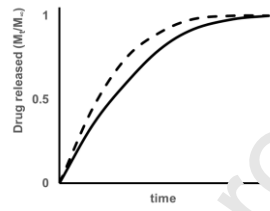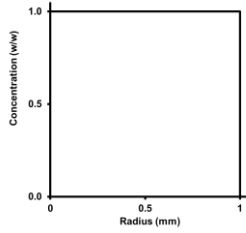
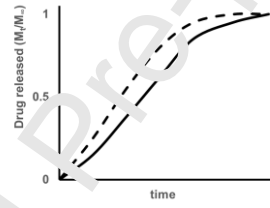Drug concentration patterns   Theoretical release profiles
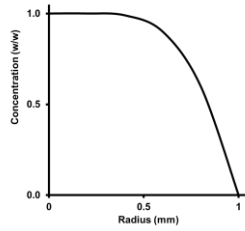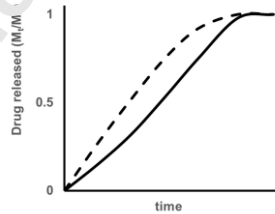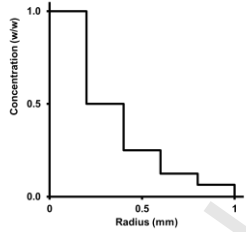
(a)

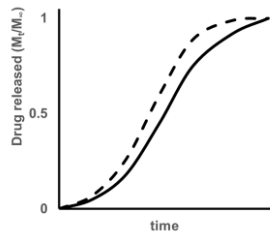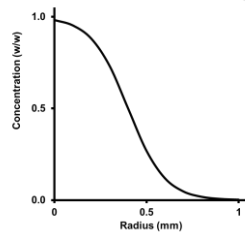

(b)

(c)

(d)

(e)

Fig. 3. Theoretical release profiles according to different drug concentration patterns of cylindrical (bold line) and spherical (dotted line) matrix systems. (a) ascending staircase concentration; (b), uniform distribution; (c) parabolic descending concentration; (d) descending staircase concentration; (e) descending sigmoidal concentration. Adapted from [44]*.*

2.2 Dynamic swelling

Patent GB2216795B described a matrix formed by cross-linked siloxanes onto which the active ingredient was loaded during the swelling process in organic solvent. Subsequent drying allowed to fix the distribution of the drug in non-homogeneous concentration within the system. The distribution of the drug was modulated by controlling the swelling time and the drying parameters [46,47].

A similar system was proposed by Forni and coworkers, who loaded ethylene:vinlylacetate copolymer (EVAc) pellets with tolbutamide [48]. The polymeric pellets were soaked in a 1 or 3% solution of the drug in chloroform, and swelling was allowed for predetermined periods of time. After evaporation of the solvent at room temperature, the drug was assayed by X-ray analysis showing non-uniform distribution with higher concentrations in the pellet center. Such a pattern was obtained by combined control of penetration of the solvent into the polymeric network and of its evaporation. A constant release of the drug was achieved over a time period of approximately 3 h.

2.3. 3D printing

3D printing is an additive manufacturing method, which offers effective solutions for customized production of even complex solid dosage forms. Various techniques are at present available for 3D printing for different purposes[49]. Solid Free-Form (SFF) technique, currently indicated as binder jetting, provides a method for the deposition of a binder solution over a layer of powder, by means of sophisticated equipment with continuous or intermittent liquid jet [50–52]. The SFF process is schematically represented in Fig. 4. Powder was rolled from a feeding device onto the surface of a build plate by a powder spreader. The thickness of the spread layer was varied from about 100 to 200 μm as a function of the type of dosage form produced. The print head then deposited the binder onto the powder layer, and the plate was lowered as to allow the successive layer to be formed. Afterwards, the powder was rolled again and the process was repeated until the dosage form was completed. The binding solution droplet size was in a 50 to 500 μm range. Servo motors were used to drive the various movements of the equiment. Suitable temperatures were selected to promote binding of the powder particles, and the loose powder was finally removed. In addition to sophisticated geometries, complex modified-release systems were thereby created with non-homogeneous drug distribution within polymeric matrices. Polyethylene oxide (PEO) and polycaprolactone were proposed as release-controlling polymers [50].
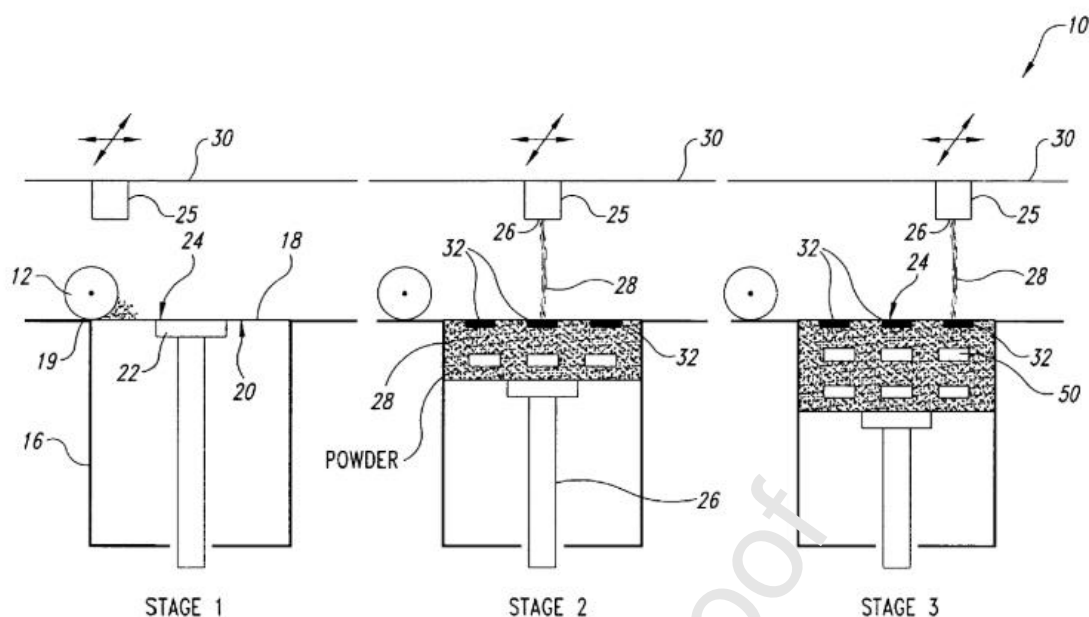
Fig. 4. Solid Free Form schematic representation. Reproduced from [50].

By the use of Fused Deposition Modeling (FDM) 3D printing, matrix systems were fabricated from HPMC [53,54]. In particular, Zhang and coworkers compared systems prepared by FDM and hot melt extrusion. More specifically, they studied the effect on the release profile of the thickness of a shell surrounding the drug-containing core and the influence of different infill percentages used during the deposition of the core (Fig. 5). Linear fitting of release data from matrices with 1.6 mm shell thickness showed that zero-order kinetics was reached for 10 h and 0.80 drug fraction released.
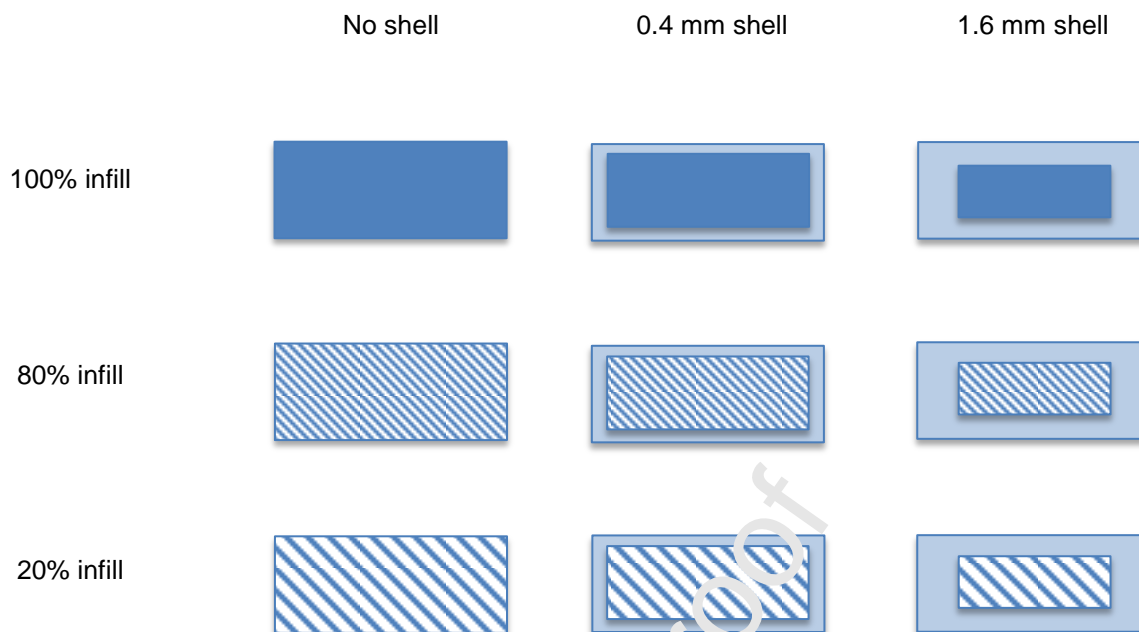
9

No shell   0.4 mm shell   1.6 mm shell

100% infill

80% infill

20% infill

Fig.5. Schematic representation of 3D printed matrices with different shell thickness and core infill percentage. Adapted from [54].

2.4. In situ photopolymerization

Diffusion-controlled laminated systems with non-uniform initial drug concentration were prepared using an *in situ* photopolymerization technique by Lu and coauthors [55,56]. The matrix was obtained by applying UV light (365 nm) at room temperature from 2-hydroxyethylene methacrylate (HEMA) as the monomer and diethylene glycol dimethacrylate (DEGDMA) as the cross-linking agent. An analytical tracer, acid orange 8, was added in water solution at different concentration. Multilaminated matrices were fabricated by layering the monomer, initiator and drug on glass microslides where polymerization occurred. After the first layer was completed, another solution was poured for polymerization of the second layer. Disks were cut from the resulting gel and coated with an impermeable film on all surfaces except for one base. The effect of the initial concentration pattern along the thickness of the gel was studied by *in vitro* release testing, and the relevant profiles were modeled for prediction of performance. The desired zero-order release was achieved by designing a special concentration pattern as a function of the distance from the external surface of the system.

2.5. Tableting

A three-layer matrix system based on HPMC (type 2208, 15.000 cps) and Phytowax (hydrogenated myristyl esters of olive oil) was proposed for prolonged release of propranolol HCl [57,58]. The lower and the upper layers contained no drug. The layered matrix was prepared by successively tableting, using flat-faced punches, different amounts of powder mixtures. Particularly, the intermediate and upper layers were tableted onto the layer previously compressed in the die cavity. The three-layer matrices provided zero-order release of the drug and showed robust results.

Zoglio and coauthors described a triple press-coated cylinder having non-uniform ("non-isomeric") concentration pattern as shown in Fig. 6 [59–61]. The system was a tablet-in-tablet with a central core and two concentric layers were prepared by employing a single-punch press. The core was manufactured by loading the relevant formulation into the tablet press equipped with flat punches of 6.3 mm in diameter. The inner coating layer was then pressed around the core using flat punches of 8.7 mm in diameter, filling the die with the amount of powder required for the lower and side portions of the coating and placing the core tablet in the center. The remaining amount of powder for the intermediate layer was then compacted to form the upper portion of the coating. The external layer of the system was applied in the same way using 11.1 mm diameter punch tooling. The core mass was 100 mg, while the inner coating was of 180 mg and the external one of 250 mg. Three different model drugs were used at concentration of 28.6%, 5.9% and 4.3% in the core, inner and outer coating, respectively, thus creating a steep gradient concentration decrease. Hypromellose (4.000 cps) was used as the release-controlling polymer at a concentration of 18% both in the core and in the coating layers. The formula also included mannitol and zinc stearate. As compared to a tablet having uniform drug concentration, the system was proved to yield an apparent linear release (Fig. 7).

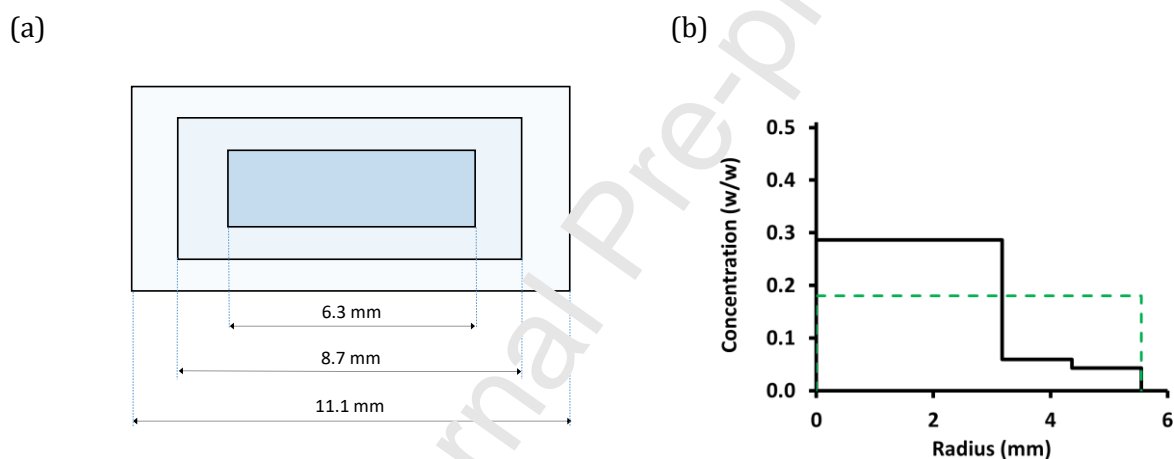(a)   (b)

Fig. 6. Schematic representation of a cylindrical matrix with non-uniform drug concentration consisting of concentric tablets (a) and profiles of drug (solid line) and polymer (dashed line) concentration along the radius. Redrawn from [60].
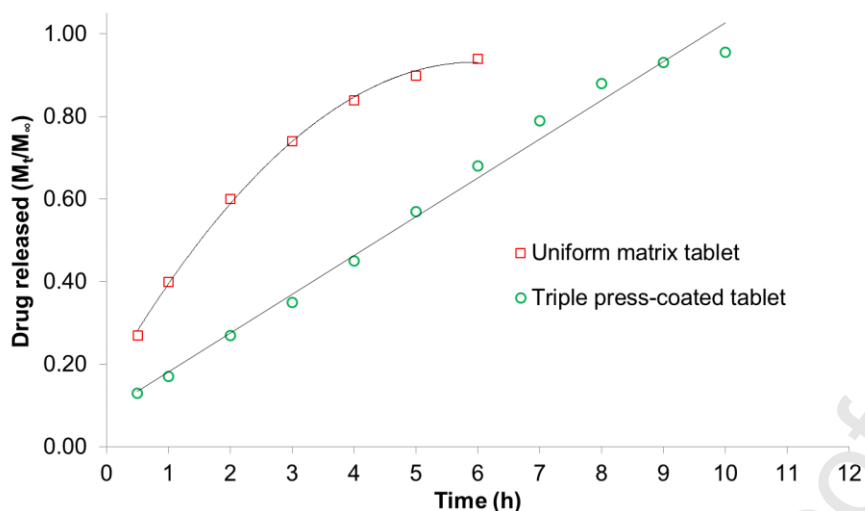
Fig. 7. Melperone HCl release profiles from a triple press-coated system having non-uniform drug concentration and from a uniform matrix tablet. Redrawn from [60]*.*

Surrounding layers loaded with drugs were applied to core tablet also by spray-coating [62,63]. In particular, the system proposed by Lee contained the drug both in a hypromellose (100.000 cps) central matrix and in an outer coating. The external layer was obtained from an aqueous-based polymeric dispersion (Eudragit® RS30D). The effect of the coating level, drug load in the outer layer, amount and type of plasticizer and percentage of talc on the release performance was evaluated. Melatonin was selected as a model drug. Unlike an uncoated matrix, the one provided with the drug-loaded coating showed data that, fitted using linear regression (r^2=0.99), resulted in zero-order release for 4 h. Alternatively, biphasic release profiles were obtained, which may be advantageous in treating pathologies with circadian symptoms. Moreover, the possibility of incorporating solubilizers and other additives into the coating dispersions could be interesting for modified release of poorly water-soluble drugs.

2.6. Solution and suspension coating

Systems having gradient drug distribution were prepared by spraying onto placebo or drug-containing cores solutions or dispersions having different drug/polymer concentration [64–70]. For this purpose, inert or hydrophilic polymers were used. Once the composition pattern was defined, the final system was constructed with a concentration gradient along the radius. In some instances, this was successful in providing zero-order release kinetics. In Fig. 8 examples of drug and polymer concentration patterns are reported.
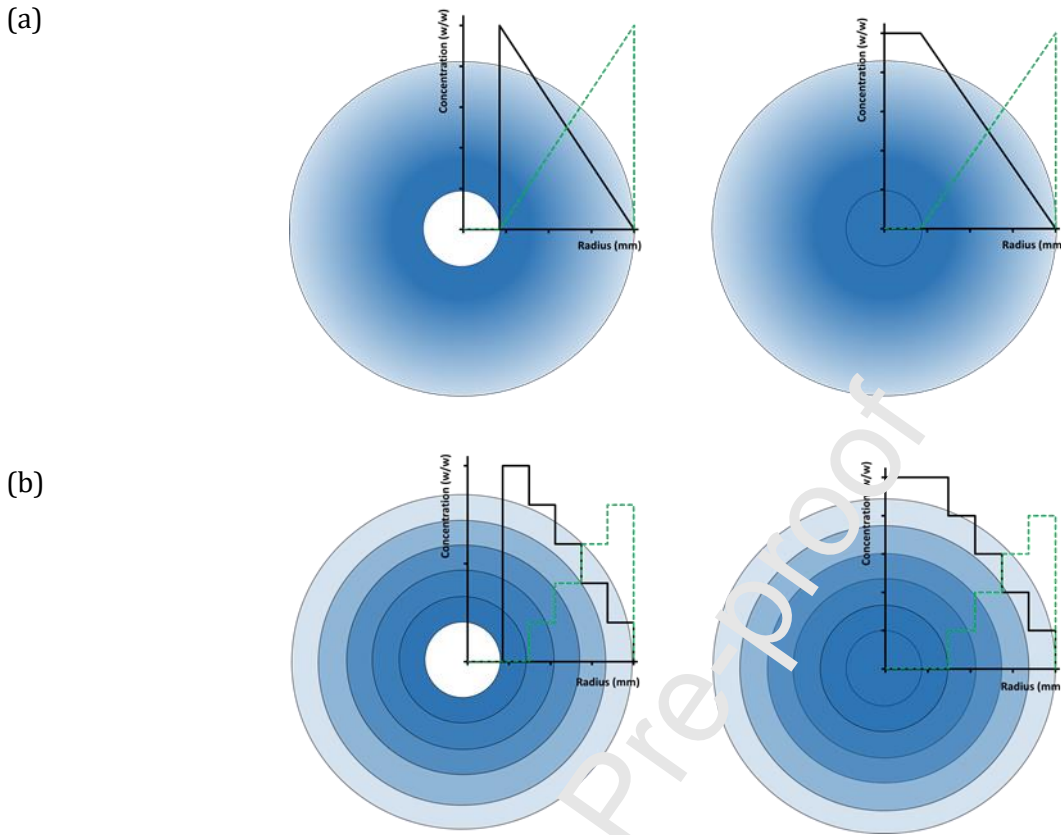
(a)

(b)

Fig. 8. Schematic representation of systems having linear (a) and staircase (b) patterns of drug (solid line) and polymer (dashed line) concentration, based on placebo (left) and drug-containing (right) cores. Adapted from [64].

Discrete layers with differing compositions were obtained by spraying specific amounts of solutions or suspensions containing the drug along with the release-controlling polymer, thereby generating a staircase concentration pattern. Because stepwise release profiles were in some cases obtained, systems with continuous decrease of drug concentration were also prepared by combining the coating components in the correct ratio by the use of two separate pumps. The polymer solution (or suspension) was pumped into a reservoir which contained the starting solution (or suspension) of the drug and polymer, and the resulting diluted coating formulation was sprayed onto the cores with a progressively reduced drug:polymer ratio [71]. A mathematical model was developed to predict the change in concentration of the active ingredient in the coating formulation as a function of the spraying rate, the pumping rate of the polymer solution/suspension into the drug-containing reservoir, and the starting drug concentration [31,71,72]. Particularly, the gradient of drug concentration vs time was described by equation:

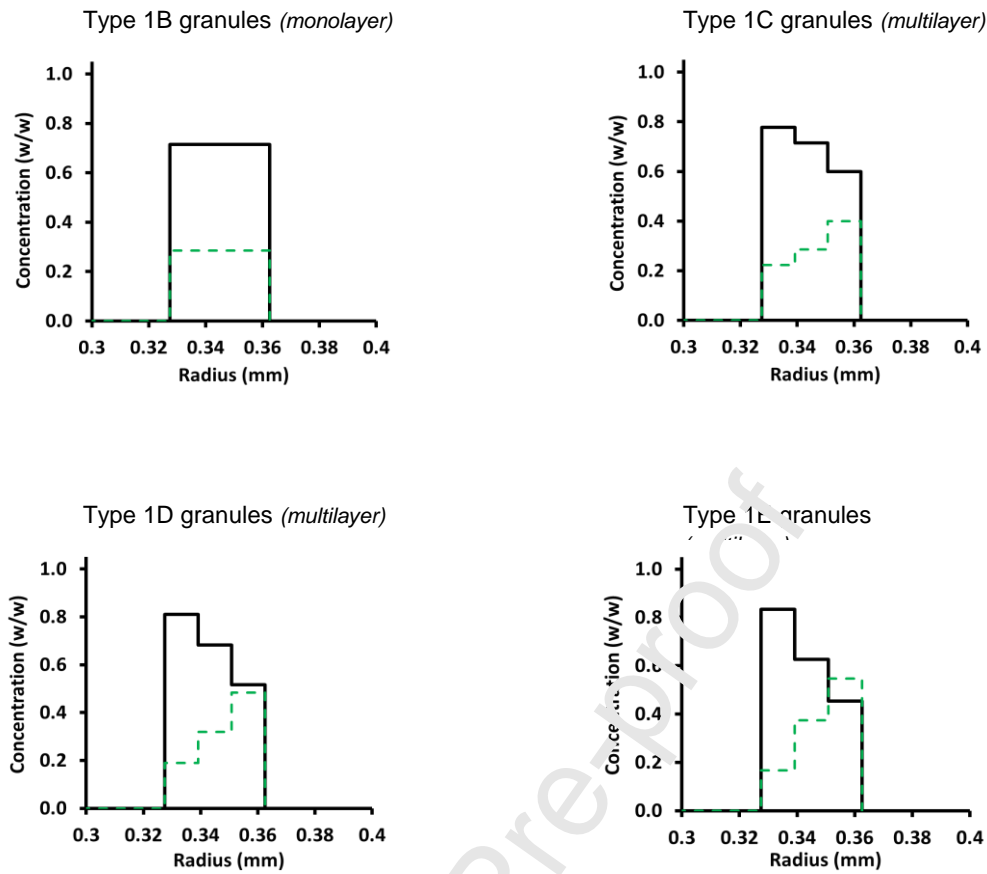$$C = C_0 \left\{ \frac{[1+(k_i+k_0)\cdot t]}{V_0} \right\}^{k_i(k_0-k_i)} \qquad (4)$$

13

where C is the concentration of the drug in the coating formulation at time t, C_0 is the initial drug concentration, k_i is the pumping rate of the polymer solution/suspension into the drug-containing reservoir, k_0 is the spraying rate of the coating formulation and V_0 is the initial volume of the drug-containing solution/suspension in the reservoir. Otherwise, the release-controlling formulation and the drug containing formulation were combined directly within the spraying apparatus [69].

Notably, when hydrophilic polymers are involved, their solubilization in water can lead to high viscosity formulations, which may be challenging for the spraying process. This would require the use of diluted systems resulting in relatively long drying phases and, consequently, processing times. Alternatively, dispersions in organic solvents can be applied, exploiting the low solubility of hydrophilic polymers in non-aqueous solvents, even if this raises problems of costs, toxicity and hazards for operators.

2.6.1 Multilayered drug-coated granules

Multilayered granules with non-uniform distribution of the drug were prepared by Wan and Lai using a fluidized bed coating process [73]. Specifically, three layers were applied onto 600-710 μm lactose granules varying in each layer the drug/polymer concentration and the polymer grade, as represented schematically in Fig. 9a. Diphenhydramine HCl was used as the model drug and methylcellulose with different viscosity was selected as the release-controlling polymer. As expected, a steeper gradient across the applied layers resulted in an overall slower release (Fig. 9b). Formulations with gradient drug distribution exhibited more effectively prolonged release as compared to the uniform control formulation.

(a)

Type 1B granules *(monolayer)*

Type 1C granules *(multilayer)*

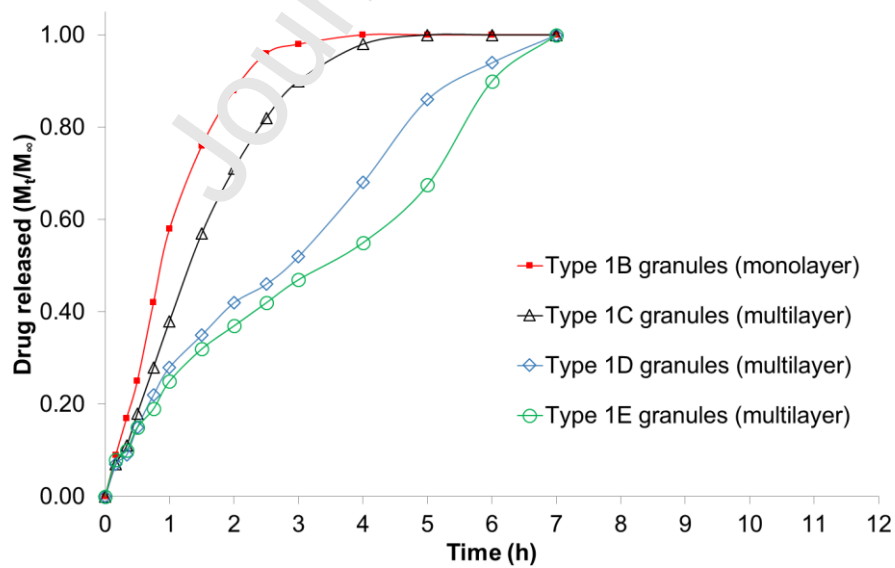Type 1D granules *(multilayer)*

Type 1E granules *(multilayer)*

(b)

Fig. 9. Schematic representation of systems having different patterns of drug (solid line) and polymer (dashed line) concentration drawn using data from [73] (a), and resulting release profiles (b). Redrawn from [73].

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2.7. Powder-layering

A novel drug delivery system with non-uniform distribution of drug, the Non-Uniform Drug Distribution Matrix (NUDDMat), was recently developed [74,75]. The system was prepared by powder-layering technique, i.e. by applying powder mixtures onto inert starting cores, thus avoiding typical issues connected with liquid-based layering processes. In this particular application of powder-layering, the use of organic solvents was avoided, and only small amounts of aqueous binding solutions were employed. Because no long drying operations were involved, the overall processing time was shortened as compared with previously described gradient systems based on hydrophilic polymers [76,77]. Such advantages would especially be evident in the case of large amounts of layered powders.

The NUDDMat consisted of five overlaid layers having drug concentrations decreasing from the inside toward the outside of the matrix according to a descending staircase function, ultimately tending to an overall apparent linear mode (Fig. 10). The nominal thickness of each layer was 315 μm aiming at a total diameter of approximately 4 mm including the cellulosic seed cores (850 μm). The percentage composition of each layer was set based on prefixed drug/polymer ratios. Paracetamol was used as the drug tracer, and hypromellose (type 2208, 100.000 cps) as the swellable release-controlling polymer. The powder layering process was run in successive steps, each corresponding to a single layer. The release profiles of the five-layer NUDDMat system and of the relevant intermediate units having 1 to 4 layers are reported in Fig. 11. Interestingly, these curves did not reflect the onion-like structure of the multilayer system having staircase concentration pattern, possibly due to partial migration of the drug during powder-layering, particularly upon contact with the aqueous binding solution, and/or penetration of the medium during release testing. The rate of release decreased as a function of the number of layers. The n values resulting from data processing by exponential Eq. (1) progressively increased thus pointing out a shift of the curves toward linearity. However, a slight burst was highlighted, which was prevented having the external layer devoid of drug. In the best proposed configuration, such a layer was also halved in thickness to avoid a short delay that was observed prior to the onset of release (Fig. 12).
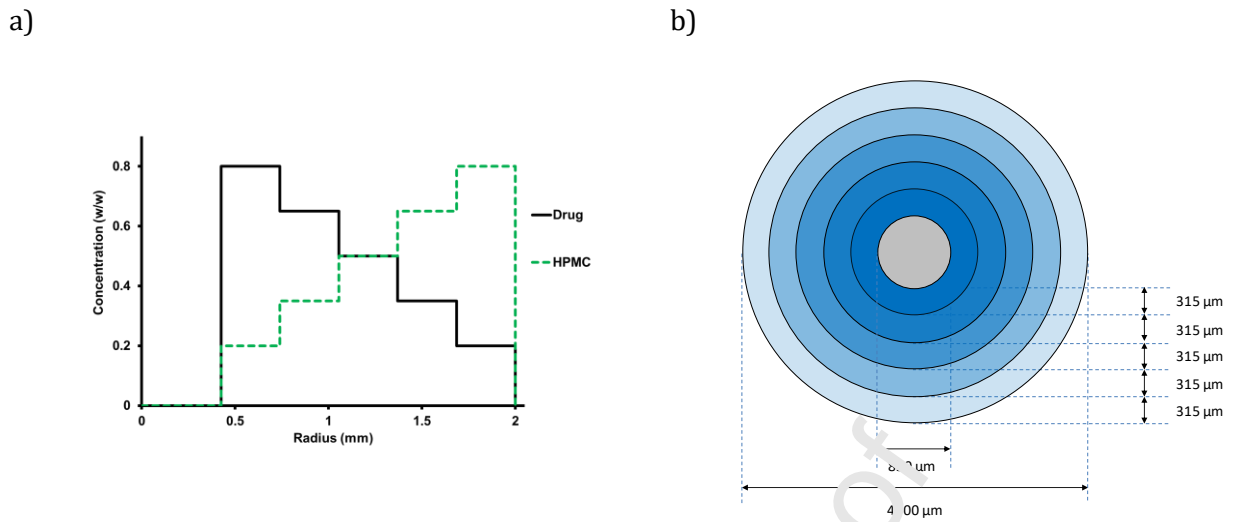
a)

b)

Fig. 10. Theoretical concentration patterns for drug and polymer along the radius (a), and schematic representation (b) of the NUDDMat system. Drug concentration is indicated by color intensity. Adopted from [74]*.*
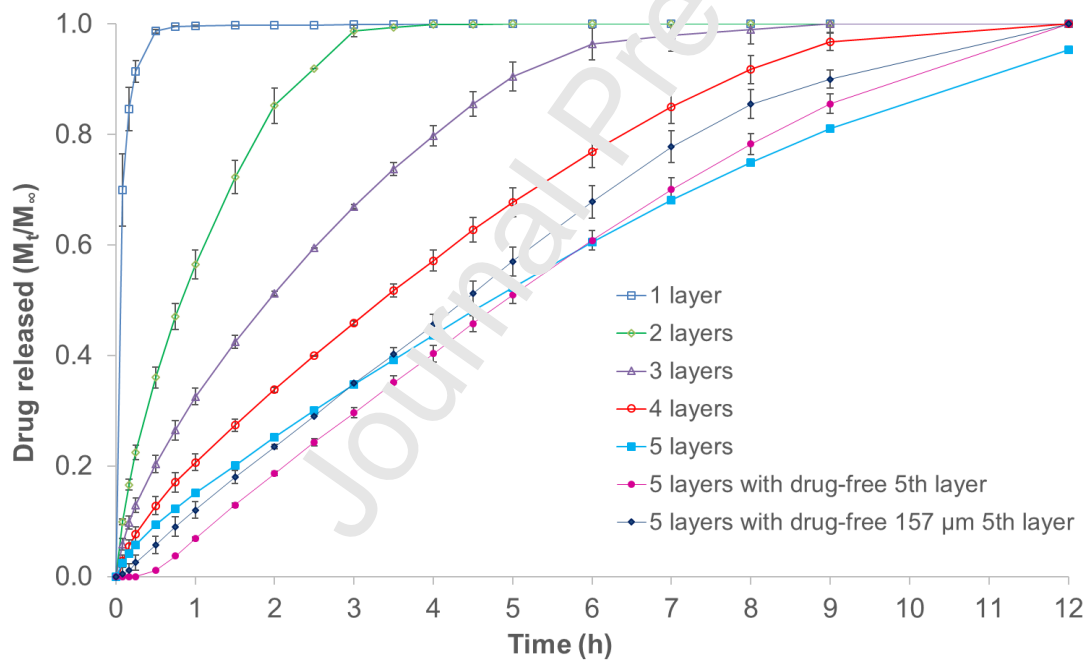

Fig. 11. Release profiles from systems NUDDMat and relevant intermediate units. Adapted from [74]
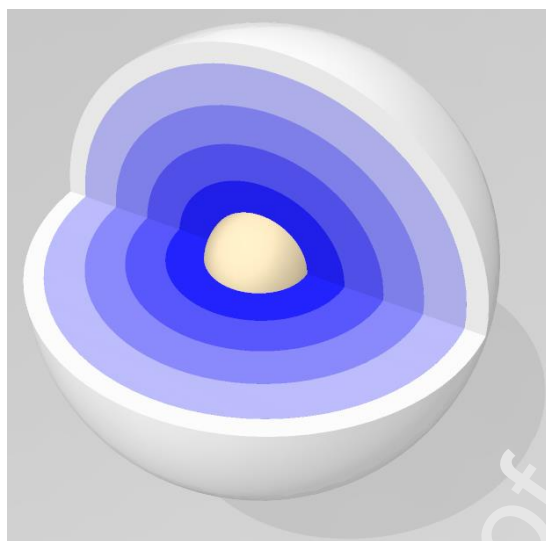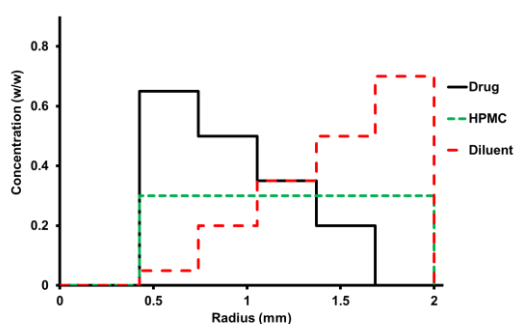
17

Fig. 12. 3D representation of the NUDDMat system having outer layer devoid of drug and halved in thickness. Drug concentration is indicated by color intensity. Redrawn from [74]

In order to reduce the concentration of hypromellose, of approximately 60%, to the percentage usually employed for prolonged-release matrices, systems with polymer content of 30% in all 5 layers, each of 315 μm, were prepared. In such a formulation, the amount of HPMC was increased in the first layer to the detriment of the drug tracer, and decreased in the other 4 layers through replacement with an insoluble (dicalcium phosphate) or a soluble (lactose) diluent (Fig. 13). Interestingly, this change was shown not impair the overall release of control. The NUDDMat system yielded zero-order release of drugs within a wide range of water solubility values irrespective of pH, provided that the drug solubility was pH-independent (Fig. 14).

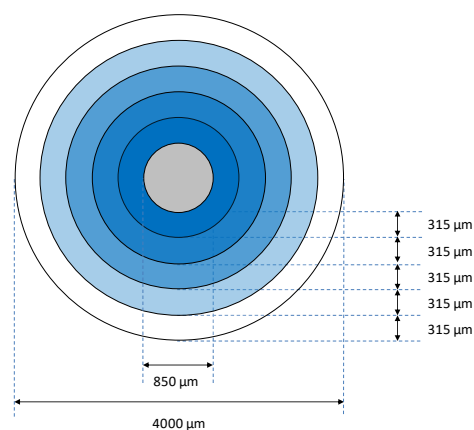a)   b)

Fig. 13. Theoretical concentration patterns for drug, polymer and diluent along the radius (a) and schematic representation (b) of the NUDDMat system having drug-free 5th layer. Drug concentration is indicated by color intensity. Redrawn from [74].
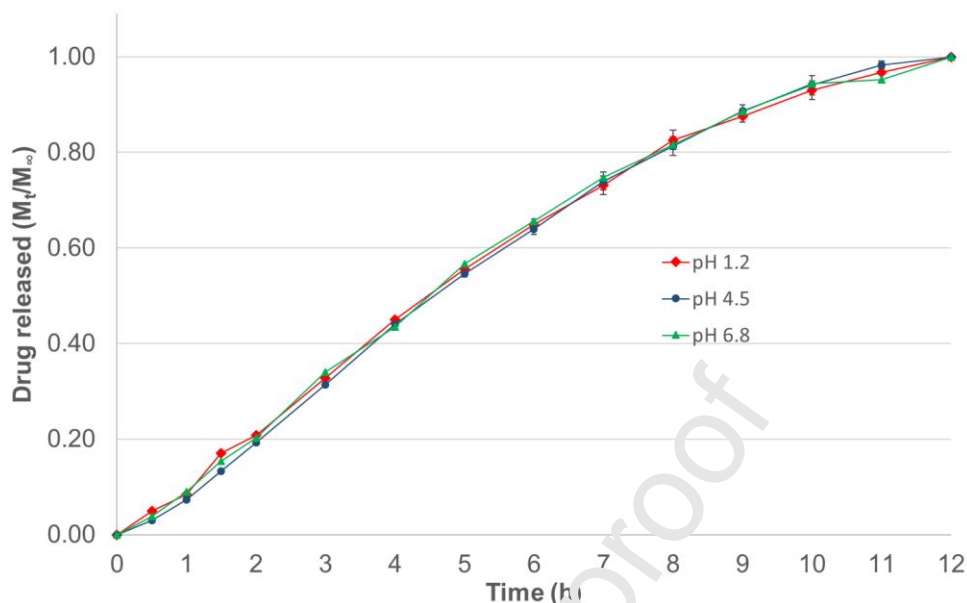
18

Fig. 14. Release profiles from paracetamol-containing NUDDMat systems tested at different pH values. Adapted from [75].

3. Analytical techniques for assessment of drug concentration patterns

As the distribution of drug and excipients within the formulation is the key factor to control drug release rate, analytical techniques used to assess the drug concentration pattern in the non-uniform distribution systems are of major importance, irrespective of the inert or hydrophilic nature of matrices. Among the techniques described in the literature for this purpose, qualitative and quantitative methods are reported.

Colored drugs or dyes allow chromatic visualization of the concentration pattern along the cross section of the units, and may ease the analytical evaluation of release [2,19,55,78,79]. Typically, dyes are used to identify the position of boundaries and their movements when the drug delivery system is exposed to penetrating fluids [19,22,80]. When florescent materials are employed, fluorescent tracing images can be acquired by applying a specific excitation wavelength [51]. Moreover, NMR imaging was used to highlight the interaction of systems with aqueous media[81].

For the quantitative analysis of the drug concentration pattern, Hildgen and McMullen collected numerous slices of the delivery system they proposed at different distances from the surface and assayed the drug in each slice spectrophotometrically. Although the method was successfully implemented with 2.5 to 10 mm long units, it could pose accuracy concerns when dealing with small-sized systems[82]. Other authors have exploited the presence in the drug tracers of atoms, such as chlorine or sulphur, capable of emitting X-rays when subjected to electron beam during SEM analysis of cross-sectioned matrices [21,48]. This method was also effective in characterizing small units. X-ray analysis allowed to collect information about drug concentration profile obtained experimentally and to compare it with the designed one. Over the years, SEM has been confirmed to be an established analytical technique for evaluation of morphology of dosage forms mainly through cross-sectional view[54,63,82]. More recently, Raman mapping analysis has been proposed to study concentration patterns of the main formulation components within the units using a confocal microscope coupled

with a laser beam source[74,83]. Particularly, the Raman spectra emitted enabled the identification of the drug, polymer and diluent employed[74]. By assigning a specific false color to each substance and calibrating the correlated peaks, colored maps were generated to trace the concentration differences. The ratio between intensity of colors assigned to the drug and the polymer, respectively, allowed the drug/polymer content ratio to be calculated and plotted against the matrix diameter. In this case, the drug concentration pattern that was pursued through stepwise powder-layering was not fully rendered. This result may not only be a consequence of analytical issues, but also could be ascribed to partial migration of the active ingredient during the layering process.

4. Conclusions

For oral prolonged-release purposes, hydrophilic matrix systems have long represented a major formulation strategy due to easy manufacturing and cost effectiveness. However, issues related to the inherent drug release performance still have to be faced. These are especially connected with the decrease in the rate of release they show over time, which hinders attainment of zero-order kinetics. Non-linear release is well known to be brought about by progressive increase in the diffusion pathway the drug has to cover to be delivered and concomitant decrease in the swelling front interface area. Moreover, an initial burst release is often observed due drug particles present on the matrix surface, which are dissolved before the polymer can fully be hydrated. Several strategies are described to achieve constant release rate for a predetermined period of time, thus reflecting in constant *in vivo* drug levels between two successive doses. The main approaches include partially-coated, geometrically-modified and/or mechanically restricted swelling systems. In addition, gradient matrices, wherein the drug concentration is increased from the outside toward the inside, have also been proposed. However, they have less broadly been exploited so far, likely because of relatively more complicated formulation designs so as to set the proper drug concentration pattern. Furthermore, rather sophisticated fabrication techniques may be needed, such as 3D printing, controlled sedimentation, photopolymerization and multilayer tableting, which have not always been widely accessible, at least until recent years, and may in some instances be hampered by scale-up limitations. Alternatively, more traditional coating techniques have been employed, although time- and energy-consuming drying phases, as well as possible stability issues, may be involved. Technical difficulties would have to be accounted for especially when dealing with aqueous spray-coating due to the use of hydrophilic polymers of high molecular mass, mostly needed to prolong the release. These indeed generate viscous solutions that would be poorly suitable for nebulization. Recently, the application of powder-layering, wherein the coating material is layered onto inert cores in the solid state, has been demonstrated as a viable approach to obtain gradient matrix systems. Such a technique could be carried out in conventional settings, thus not requiring any special equipment, and would circumvent most of the above-mentioned drawbacks related to liquid-based processes [84,85]. For these reasons, powder-layering could make non-uniform drug distribution technologies using hydrophilic swellable polymers more convenient and attractive.

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