

Journal of Coastal Life Medicine

Journal homepage: www.jclmm.com



Document heading

doi:10.12980/JCLM.2.2014JCLM-2013-0006

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Drug release characteristics of dosage forms: a review

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PEER REVIEW

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Comments

This study is promising that deals with the release characteristics of dosage forms. Assessment of pattern of release of drug is a innovative point. The apparatus and the mathematical models have been given in combination, this would be an ease for the further study for researchers.

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ABSTRACT

Area of drug delivery is vast, and various advances have been made in the medical field. Besides the versatility in the dosage forms, various orders for the drug release are known, which includes zero order, first order, Higuchi model, Hixon Crowell model and Korsmeyer Peppas model. *In vitro* dissolution is recognized as an important element in the development of drug. The nature of the drug such as its shape, crystallinity, particle size and solubility reflects the kinetics of the drug. Various models are used to study the dissolution profiles of the new drug substances. Qualitative and quantitative changes in the drug alters the drug release and performance that is action of drug in the body, which is *in vivo* performance. Various model dependent methods and model independent methods have been taken into consideration for studying the drug release kinetics.

KEYWORDS

Dissolution, Kinetics, Order, Delivery system, Models

1. Introduction

Drug release is the process by which a drug product is subjected to absorption, distribution, metabolism, and excretion, eventually becoming available for pharmacological action^[1].

2. Modified release dosage forms

Modified release dosage forms defined by United States Pharmacopoeia as those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms^[2].

2.1. Delayed release

Delayed release indicates that the drug is not being released immediately but at later time.

2.2. Repeat action

Repeat action indicates that an individual dose is released fairly soon after administration, and the second or third doses are subsequently released at intermittent intervals.

2.3. Prolonged release

Prolonged release indicates that the drug is provided for absorption over a longer period of time than that of a conventional dosage form. The onset of action is also delayed due to an overall slower release of the drug from the dosage form.

2.4. Extended release

Extended release refers to the slower release of the drug so that plasma concentrations are maintained at a therapeutic level for an extended period of time (usually between 8 and 12 h).

2.5. Controlled release

The drug is released at a constant (zero order) rate and provides plasma drug concentration that remains invariant with time.

2.6. Sustained release

The release of the drug is retarded for a delayed and/or prolonged period of time (to slow first order release) in the systemic circulation. The onset of action and the therapeutic

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Article history:

Received 30 Dec 2013

Received in revised form 9 Jan, 2nd revised form 15 Jan, 3rd revised form 19 Feb 2014

Accepted 17 Apr 2014

Available online 28 Apr 2014

efficacy of the drug are often sustained in such delivery systems[3].

The capability to deliver high effective dosages to specific sites in the human body has become the holy grail of drug delivery research. Drugs with proven effectiveness under *in vitro* investigation often reach a major roadblock under *in vivo* testing due to lack of an effective delivery strategy. In addition, many clinical scenarios require delivery of agent that are therapeutic at the desired delivery point, but otherwise systemically toxic[4].

The nonspecific distribution of drugs is wasteful and hampers the clinical usefulness of most of these agents after their systemic administration in the body. It increases the incidence of toxic reactions thereby narrowing down the therapeutic index of the drug[5].

Another problem associated with systemic drug absorption is the inability to target a specific area of the body. So systemic drug therapy is an undesirable way to cure a local disease, hence localization of agent to the diseased area is a more suitable and rational answer to this problem.

Dissolution from a dosage form involves two steps, liberation of the drug from the formulation matrix (disintegration) followed by the dissolution of the drug (solubilization of the drug particles) in the liquid medium. The overall rate of dissolution depends on the slower of these two steps[6]. *In vitro* dissolution tests for solid oral dosage forms are used:

- (1) To assess the quality of a drug product.
- (2) To assess the stability of the drug product.
- (3) To ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process.
- (4) To develop new formulations. In formulation development, dissolution testing can aid in the selection of excipients, helping optimize the manufacturing process, and enable formulation of the test product to match the release of the reference product[7].

2. Apparatus classification in the United States Pharmacopoeia

- Apparatus 1 (rotating basket)
- Apparatus 2 (paddle assembly)
- Apparatus 3 (reciprocating cylinder)
- Apparatus 4 (flow-through cell)
- Apparatus 5 (paddle over disk)
- Apparatus 6 (cylinder)
- Apparatus 7 (reciprocating holder)[3]

2.1. Rotating basket

The performances of dissolution apparatus depends on the hydrodynamics of the fluid. It is used for the dosage forms such as microspheres that provide sustained release. The

temperature conditions are normal temperature of body that is 37 °C and the volume of the media is taken as 900 mL[8].

Basket consists of two parts: a) Vessel: it is made of borosilicate glass with semi hemispherical bottom having nominal capacity of 1000 mL; b) Vent with a shaft: it is made up of stainless steel 316 and rotates smoothly without any wobble. Basket is made up of stainless steel 316 coated with gold coating up to 0.0001 inch.

Water bath is maintained at (37 ± 0.5) °C and is used for capsules, tablets, suppositories, floating dosage forms[9]. Figure 1 shows the dimensions of rotating basket type apparatus. Table I shows the composition of various Medias used.

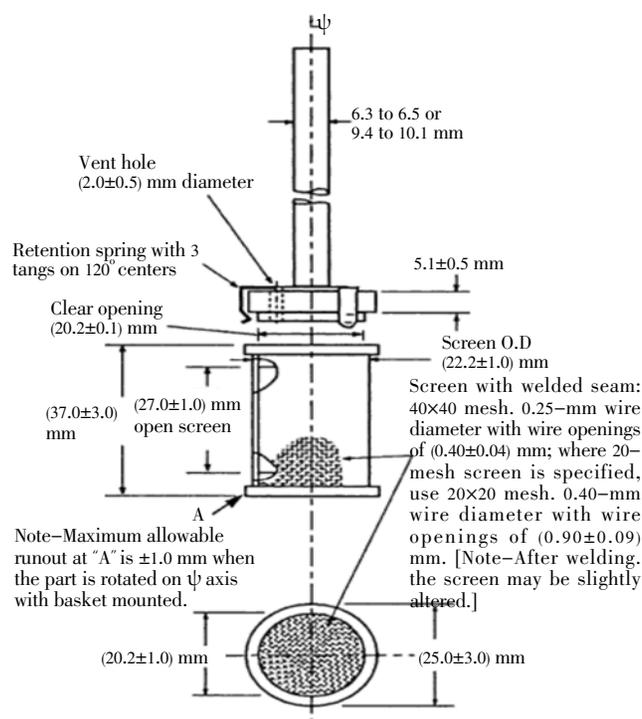


Figure 1. Dimensions of basket type apparatus.

2.2. Paddle type

The apparatus "Paddle" consists of a cylindrical vessel of suitable glass with a hemispherical bottom and with capacity of 1000 mL. The details are listed as follows: 1) Vessel: the vessel is covered to prevent evaporation of the medium; 2) Shaft: the blade passes through shaft so that bottom of blade fuses with bottom of shaft; 3) Stirring elements: these are made of teflon or stainless steel; 4) Water bath: it is maintained at (37 ± 0.5) °C; 5) Sinkers: it is made up of platinum wire used to prevent capsule/tablet from floating[10]. Figure 2 shows the dimensions of paddle type apparatus.

The paddle apparatus consists of a special, coated paddle that minimizes turbulence due to stirring. The paddle is attached vertically to a motor that rotates at a controlled speed of 40 r/min.

Table 1

Composition of dissolution medias.

Medias used	Composition
Hydrochloric acid (0.1 mol/L)	3.6 g of HCl corresponding to 8.3 mL HCl per 1000 mL of aqueous solution
Acetate buffer solution (pH 4.5)	2.9 g of sodium acetate trihydrate and 1.6 g of glacial acetic acid. Added quantity sufficient water to 1000 mL
Phosphate buffer (pH 4.5)	13.61 g monobasic potassium hydrogen phosphate dissolved in 750 mL water. Adjust the pH to 4.5 with 0.1 mol/L HCl or 0.1 mol/L sodium hydroxide. Added quantity sufficient water to 1000 mL
Intestinal fluid (pH 7.5)	250 mL of a solution containing 6.8 g of monobasic potassium phosphate. Added 190 mL of 0.2 mol/L sodium hydroxide. Added quantity sufficient water to 1000 mL

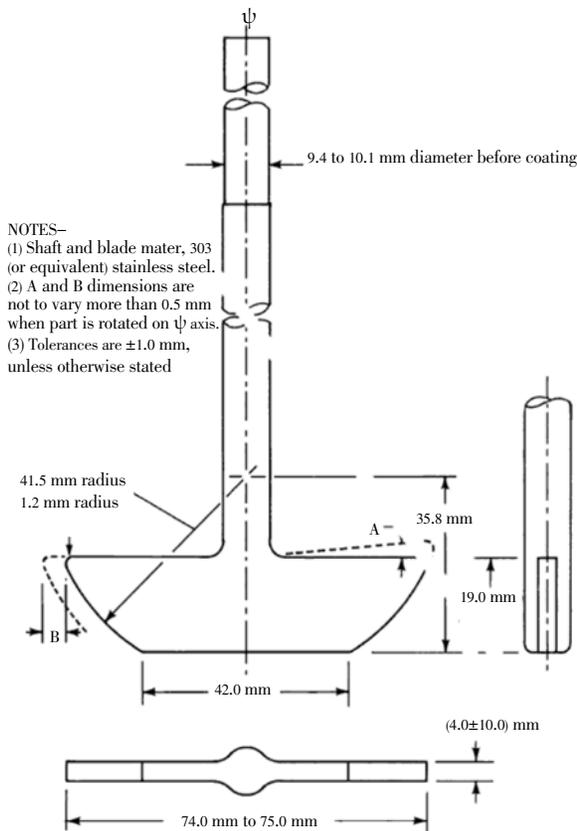


Figure 2. Dimensions of paddle type apparatus.

2.3. Reciprocating type

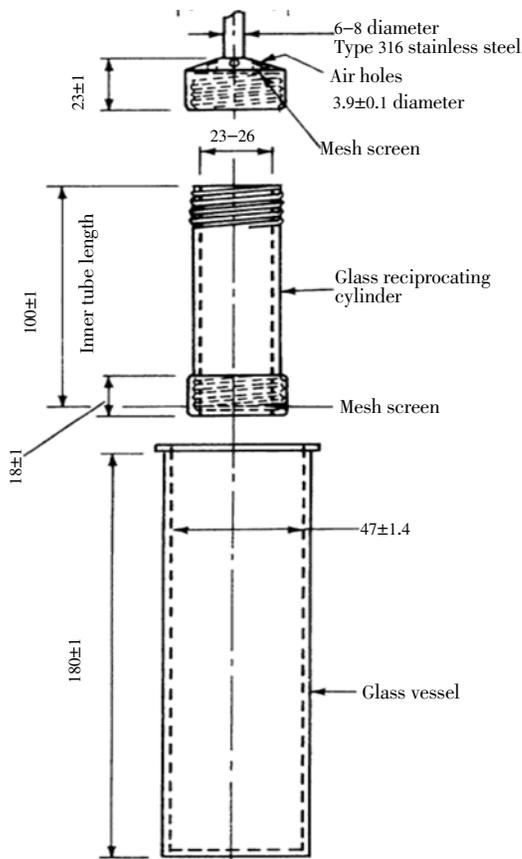


Figure 3. Dimensions of reciprocating apparatus.

The development of reciprocating type was based on the recognition of the need to establish *in-vitro* and *in-vivo*

correlation.

The design incorporates the hydrodynamic features from the rotating basket method and provides agitation and media composition changes during a run as well as full automation of the procedure.

Reciprocating type can be especially useful in cases where one or more pH/buffer changes are required in the dissolution testing procedure, for example, enteric-coated/sustained release dosage forms.

Reciprocating type possess the features such as biorelevance, flexibility, compliance, easy configuration, automatic sampling and reporting^[11]. Figure 3 shows the dimensions of reciprocating apparatus and Figure 4 shows the dimensions of reciprocating apparatus for microspheres.

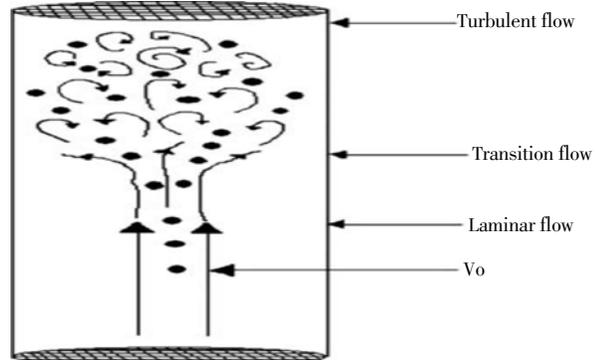


Figure 4. Reciprocating apparatus for microspheres.

2.4. Flow through cell

Designed specifically for use of lipidic products such as fat-based suppositories and oil-filled soft gelatin capsules, this flow cell solves the problems of floating and the formation of a lipidic layer on the surface of the dissolution medium.

The cell consists of three compartments: 1) The lower part is made up of two adjacent chambers connected to an overflow device. As the dissolution medium passes through chamber, it is subjected to an upward flow. The flow in chamber is directed downward to an exit that then leads upward to a filtering assembly; 2) The middle part of the cell has a cavity designed to collect lipophilic excipients that float on the dissolution medium. A metal mesh is used as a rough filter; 3) The upper part holds the filter in place. The sample is then collected and analyzed for drug release content. Figure 5 a) shows apparatus for dosage forms such as medicated chewing gums and Figure 5 b) shows the flow through apparatus for semisolid products respectively.

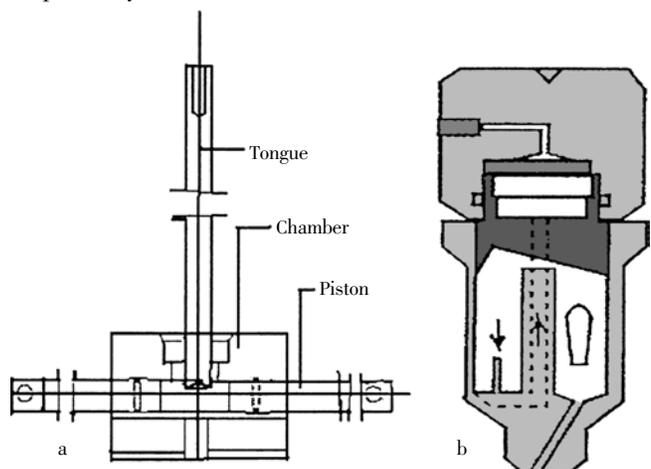


Figure 5. a) Apparatus for dosage forms such as medicated chewing gums. b) Flow through apparatus for semisolid products.

Figure 6 shows the dimensions of flow through cell apparatus.

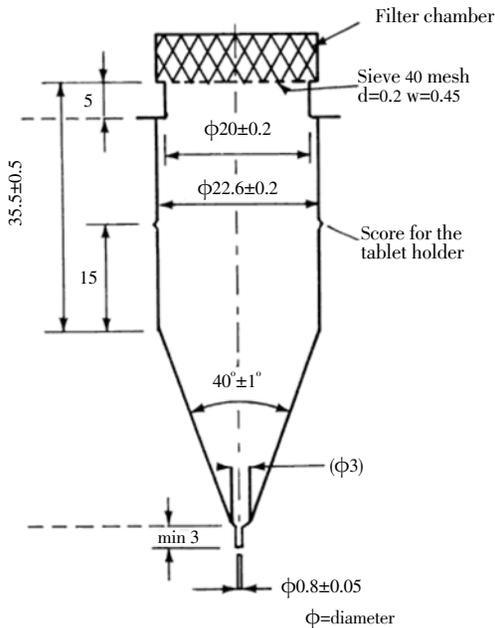


Figure 6. Dimensions of flow through cell apparatus.

2.5. Paddle over disc

Paddle over disc is designed for the transdermal drug delivery systems. The transdermal patch is placed between a glass disc and an inert polytetrafluoroethylene mesh. Transdermal testing is carried out at 32 °C to show the lower temperature of the skin. Figure 7 shows the dimensions of paddle over disc apparatus.

kinetic modeling characteristics.

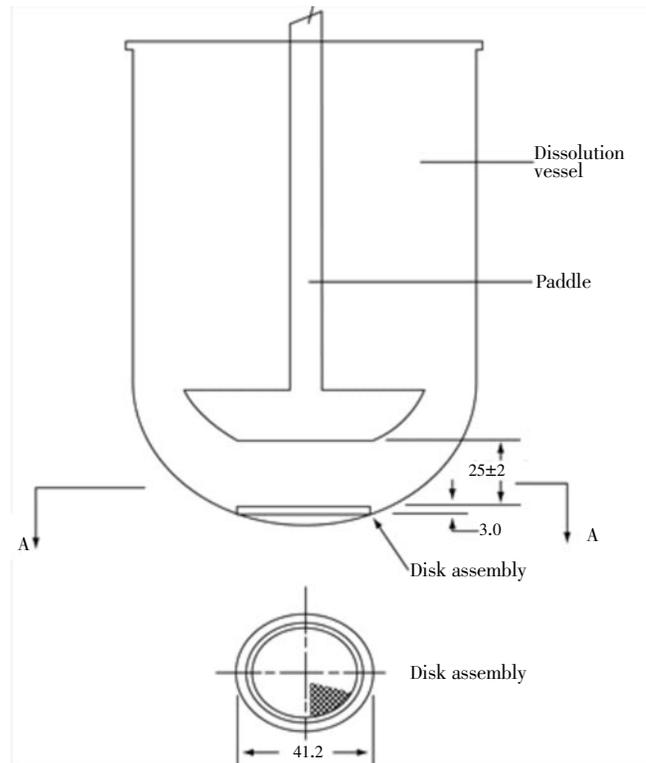


Figure 7. Paddle over disc.

3. Mathematical models

Mathematical models consist of zero order release kinetics, first order model, Higuchi model, Hixon Crowell model and Korsmeyer Peppas model (Figure 8 to 11). Table 2 shows the

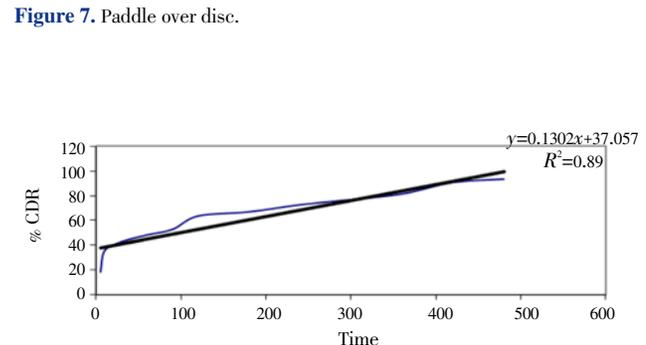


Figure 8. Zero order plot.

Table 2

Kinetic modeling of drug delivery systems.

Drug release model	Equation	Drug delivery device	Applications	Graph plot
Zero order	$Q=Q_0+K_0t$ where Q is the amount of drug released, Q_0 is the initial amount of drug in solution and K_0 is the zero order release constant.	Constant drug release from a drug delivery device such as oral osmotic tablets, transdermal systems, matrix tablets with less water-soluble drugs	In classes of medicines, for antibiotic delivery, heart and blood pressure maintenance, analgesics and antidepressants	%CDR vs time [12] (Figure 8)
First order	$\log C=\log C_0-kt/2.303$ where C_0 is the initial concentration of the drug, C is the final concentration of the drug, k is the constant and t is time.	For dosage forms containing water soluble drugs in porous matrix	In elimination and absorption of drugs	$\log\%$ CDR of amount remaining vs time [13]. (Figure 9)
Hixon Crowell model	$Q_0^{1/3}-Q_t^{1/3}=kt$ where $Q_0^{1/3}$ is initial amount of drug in the tablet, $Q_t^{1/3}$ is amount of drug released at time, k is constant and t is time.	Sustained release tablets	In cases where particle size and surface area changes	Cube root of amount remaining vs time (Figure 10)
Higuchi model	$Q=AV^{1/2}(2C-C_0)C_s t$ where Q is the amount of drug released in time t per unit area A , C is the initial drug concentration, C_s is the drug solubility in the matrix media, D is the diffusivity of the drug molecules in the matrix substance.	Hydrophilic matrix tablets	It describes the drug dissolution from several types of modified release pharmaceutical dosage forms such as transdermal drug delivery system and matrix tablets with water soluble drugs	%CDR v.s. $\sqrt{\text{time}}$
Korsmeyer peppas model	$M_t/M_0=k^n M_0/n$ M_t/M_0 =fraction of drug released, n =diffusional exponent, k = rate constant (min^{-n}).	Drug release from polymeric systems	Diffusional release from polymeric films	$\log\%$ CDR vs \log time [14-16]. (Figure 11)

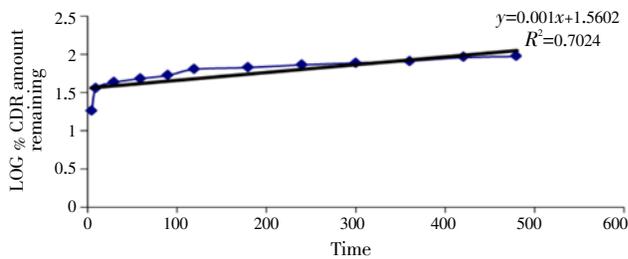


Figure 9. First order model.

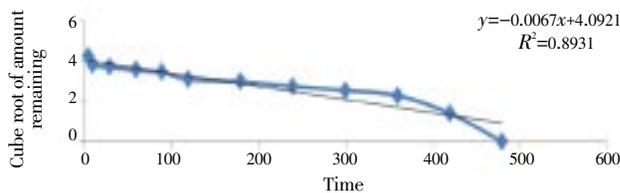


Figure 10. Hixon Crowell model.

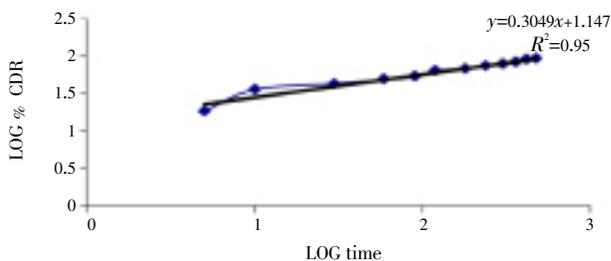


Figure 11. Korsmeyer Peppas model.

4. Conclusion

Kinetic modeling reviews on drug release show that various models have been established to describe the relationship between drug dissolution and geometry on drug release patterns mathematically. The physicochemical properties of the drug as well as polymer and the drug to polymer ratio govern the release of drug from the formulation and thus, modify the release kinetics accordingly.

Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

Area of drug delivery has covered a vast area. Besides the versatility in the dosage forms, various orders for the release are known which includes zero order, first order, Higuchi model, Hixon Crowell model and Korsmeyer Peppas model.

Research frontiers

The paper describes the drug release mechanism for the dosage forms and the dissolution apparatus used for a particular dosage form. For example, it has been cited that for microspheres basket type apparatus is used.

Related reports

Various apparatus have been discussed in United States Pharmacopeia. but in the present short review, previous studies have been compiled up by authors.

Innovations and breakthroughs

All the models have been complied which provides ease for the researchers to work further towards the novel drug delivery system.

Applications

Drug release is assessed by various mathematical models and apparatus which are discussed, thus it can be clarified either the drug is sustained release or delayed release through the present paper.

Peer review

This study is promising that deals with the release characteristics of dosage forms. Assessment of pattern of release of drug is a innovative point. The apparatus and the mathematical models have been given in combination, and this would be a ease for the further study for researchers.

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