INTERNATIONAL JOURNAL OF RECENT ADVANCES IN PHARMACEUTICAL RESEARCH
JANUARY 2014; 4(1): 6-17

DRUG RELEASE CHARACTERISTICS OF DOSAGE FORMS: A REVIEW

SATINDER KAKAR*, RAMANDEEP SINGH[1], ALOK SEMWAL[1]

**DEPARTMENT OF PHARMACY, DOON VALLEY INSTITUTE OF PHARMACY AND MEDICINE, KARNAL, HARYANA, INDIA.*
[1]DEPARTMENT OF PHARMACY, HIMACHAL INSTITUTE OF PHARMACY, PAONTA SAHIB, H.P, INDIA.

ABSTRACT

Area of drug delivery has covered a vast area. Various advances have been made in the medical field. 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. *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, 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

1.0. INTRODUCTION

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

1.1 MODIFIED RELEASE DOSAGE FORMS (MR)

Modified release dosage forms defined by USP 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].

**Correspondence*
Satinder Kakar
Department of pharmacy,
Doon valley institute of pharmacy and medicine,
Karnal, Haryana, India
E-Mail: satinder.kakkar5@gmail.com
Tel no: 9736922900

1.1.1 DELAYED RELEASE (DR)

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

1.1.2 REPEAT ACTION (RA)

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

1.1.3 PROLONGED RELEASE (PR)

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

1.1.4 EXTENDED RELEASE (ER)

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).

1.1.5 CONTROLLED RELEASE (CR)

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

1.1.6 SUSTAINED RELEASE (SR)

The release of the drug is retarded for a delayed and/or prolonged period of time (slow first order release) in the systemic circulation. The onset of action and the therapeutic 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 attack a local disease, hence localization of agent to the diseased area is more suitable and rationale 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]. I*n 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, help 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 USP

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]

2.1ROTATING BASKET

The performances of dissolution apparatus depends on the hydrodynamics of the fluid. It is used for the dosage forms such as microspheres that are to provide sustained release. The temperature conditions are of normal body temperature of body that is thirty seven degrees Celsius and the volume of the media is taken as 900 ml[9].

Basket consists of two parts:

1. The top part, with a vent, is attached to the shaft. It is fitted with three spring clips that allow removal of the lower part so that the preparation being examined can be placed in the basket.

2. The lower detachable part of the basket is made of welded-seam cloth, with a wire thickness of 0.254 mm diameter and with 0.381 mm square openings, formed into a cylinder with a narrow rim of sheet metal around the top and the bottom. If the basket is to be used with acidic media, it may be plated with a 2.5-µm layer of gold [10]. Figure 1 show the dimensions of Rotating basket type apparatus.

2.1.1 DISSOLUTION MEDIAS USED

TABLE I COMPOSITION OF DISSOLUTION MEDIAS

MEDIAS USED	COMPOSITION
0.1 N Hydrochloric acid	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. q.s. 1000 ml with water
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 N HCl or 0.1 N 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 N Sodium hydroxide. Added quantity sufficient water to produce 1000 ml

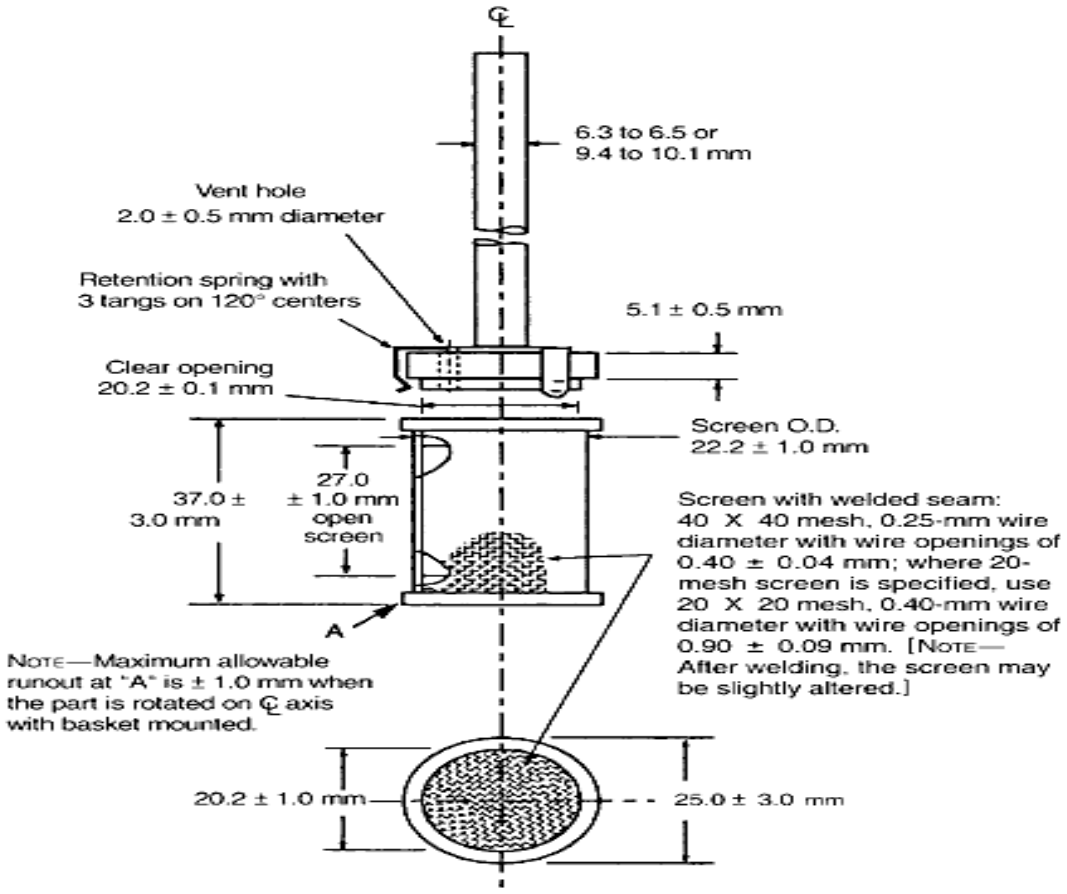

FIGURE 1: DIMENSIONS OF BASKET TYPE APPARATUS

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.

1. The vessel is covered to prevent evaporation of the medium with a cover that has a central hole to accommodate the shaft of the stirrer and other holes for the thermometer and for devices for withdrawal of liquid.

2. The stirrer consists of a vertical shaft with a blade at the lower end. The blade is constructed around the shaft so that it is flush with the bottom of the shaft. When placed inside the vessel, the shaft's axis is within 2mm of the axis of the vessel and the bottom of the blade is 25 ± 2mm from the inner bottom of the vessel.

3. The upper part of the shaft is connected to a motor provided with a speed regulator. The apparatus is placed in a water-bath that maintains the dissolution medium in the vessel at 37 ± 0.5 °C [11]. Figure 2 shows the dimensions of paddle type apparatus

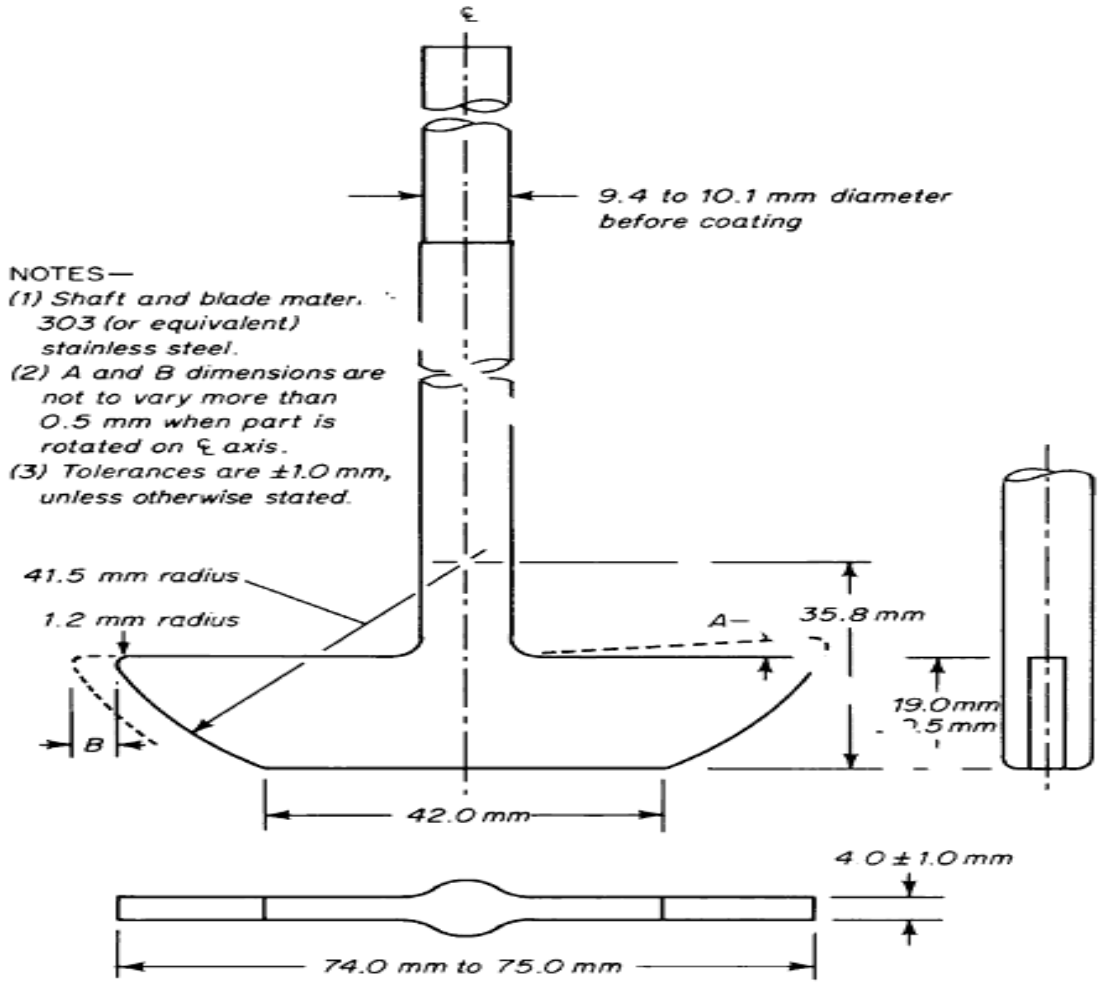

FIGURE 2: DIMENSIONS OF PADDLE TYPE APPARATUS

2.3 RECIPROCATING TYPE

1. The development of reciprocating type was based on the recognition of the need to establish IVIVC.

2. 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. 3. It 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.

It possess the features such as biorelevance, flexibility,compliance,easy configuration,automatic sampling and reporting [12]. Figure 3 shows the dimensions of reciprocating apparatus and figure 4 shows the dimensions of reciprocating apparatus for microspheres.

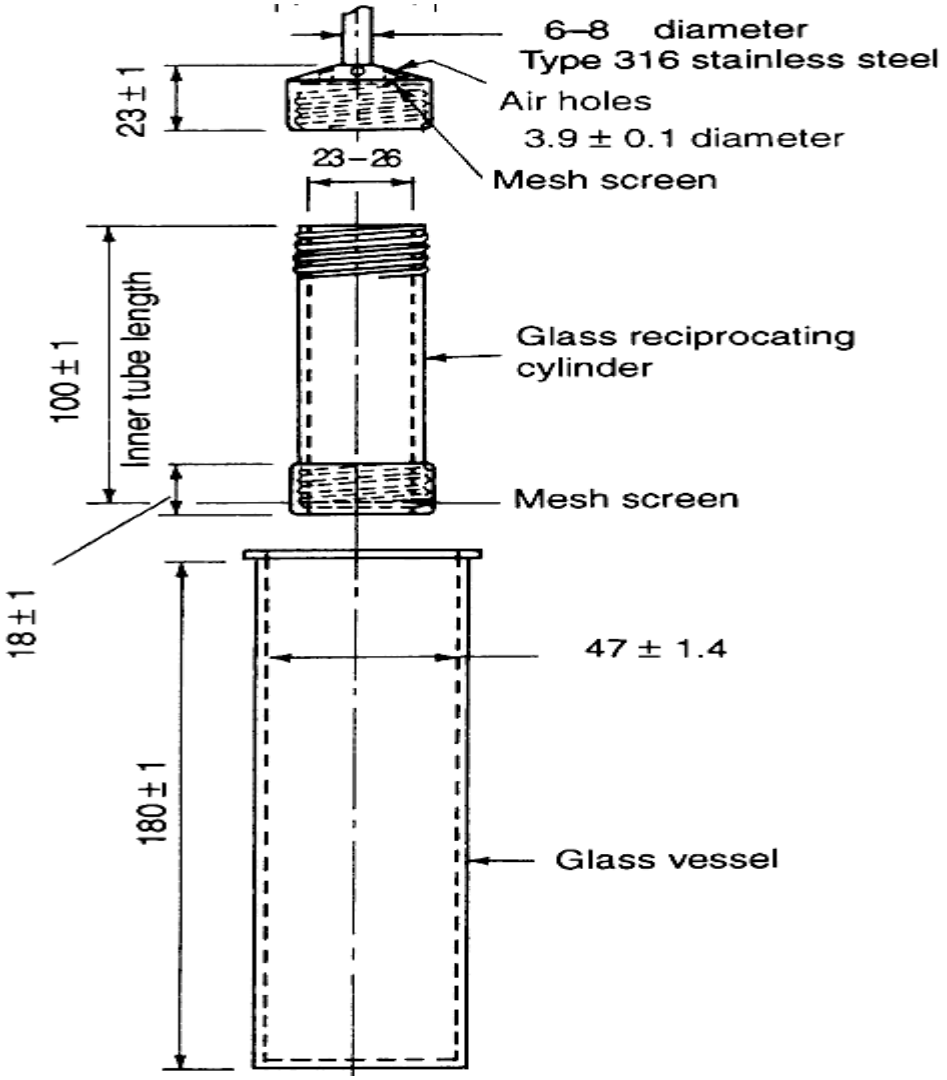

FIGURE 3: DIMENSIONS OF RECIPROCATING APPARATUS

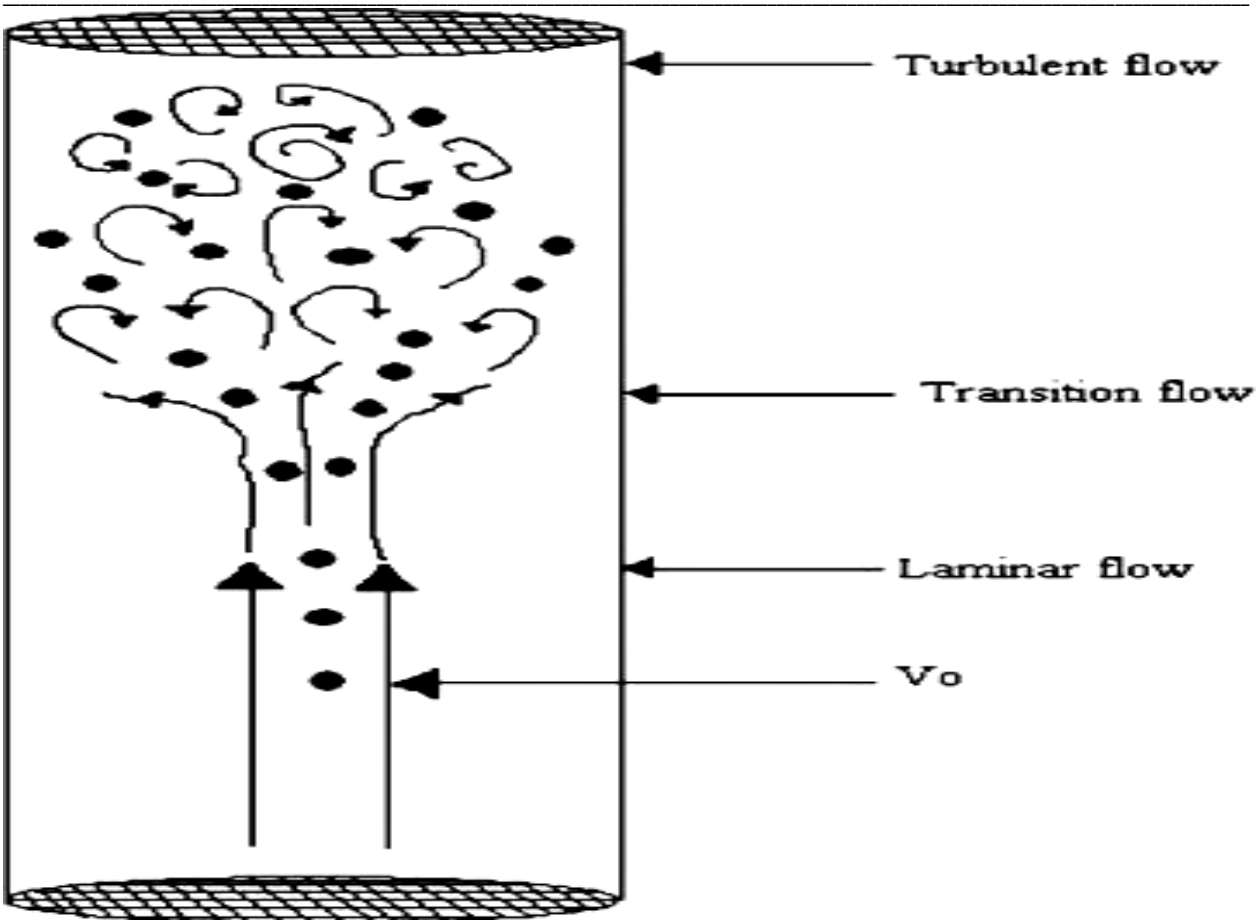

FIGURE 4: RECIPROCATING APPARATUS FOR MICROSPHERES

2.4 FLOW THROUGH CELL

Designed specifically for use with 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) flow through apparatus for semisolid products respectively.
Figure 6 shows the dimensions of flow through cell apparatus

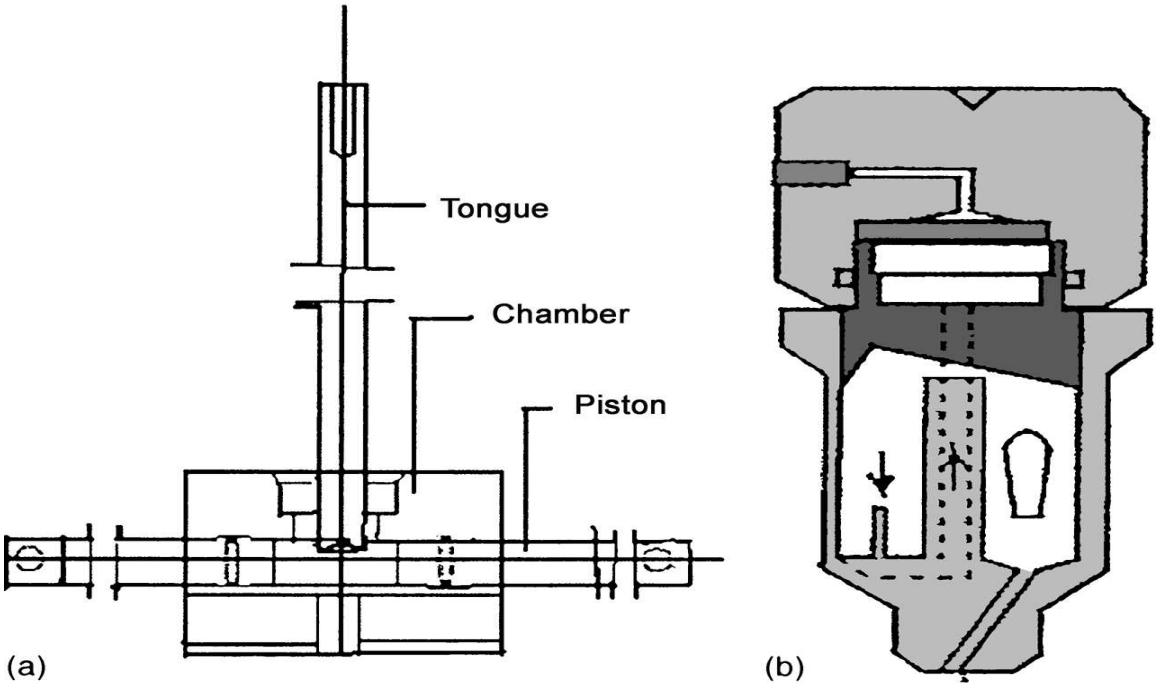

FIGURE 5: A) APPARATUS FOR DOSAGE FORMS SUCH AS MEDICATED CHEWING GUMS B) FLOW THROUGH APPARATUS FOR SEMISOLID PRODUCTS

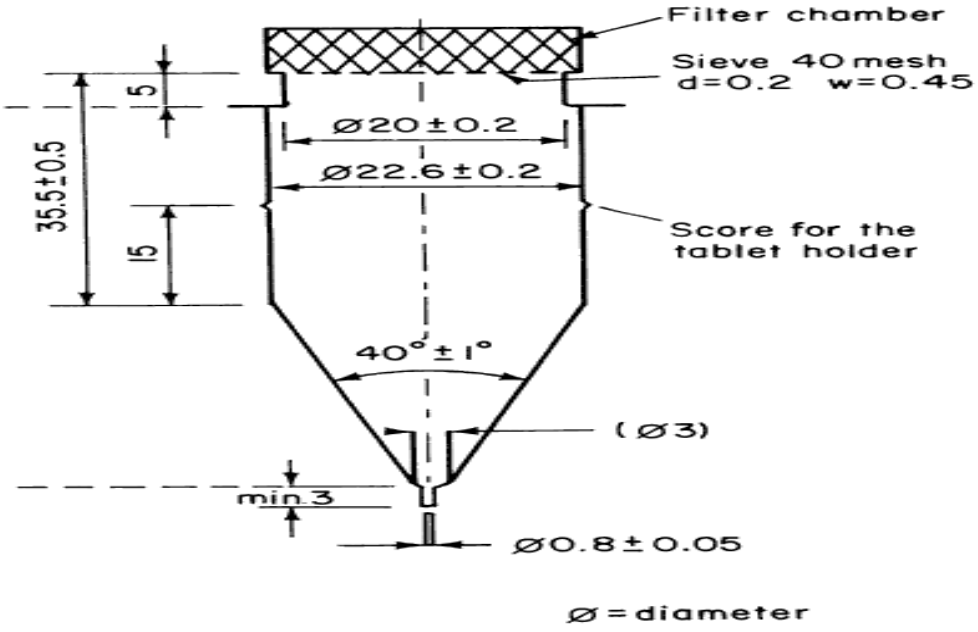

FIGURE 6: DIMENSIONS OF FLOW THROUGH CELL APPARATUS

2.5 PADDLE OVER DISC

1. Designed for the transdermal drug delivery systems
2. The transdermal patch is placed between a glass disc and an inert PTFE mesh.
3. 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

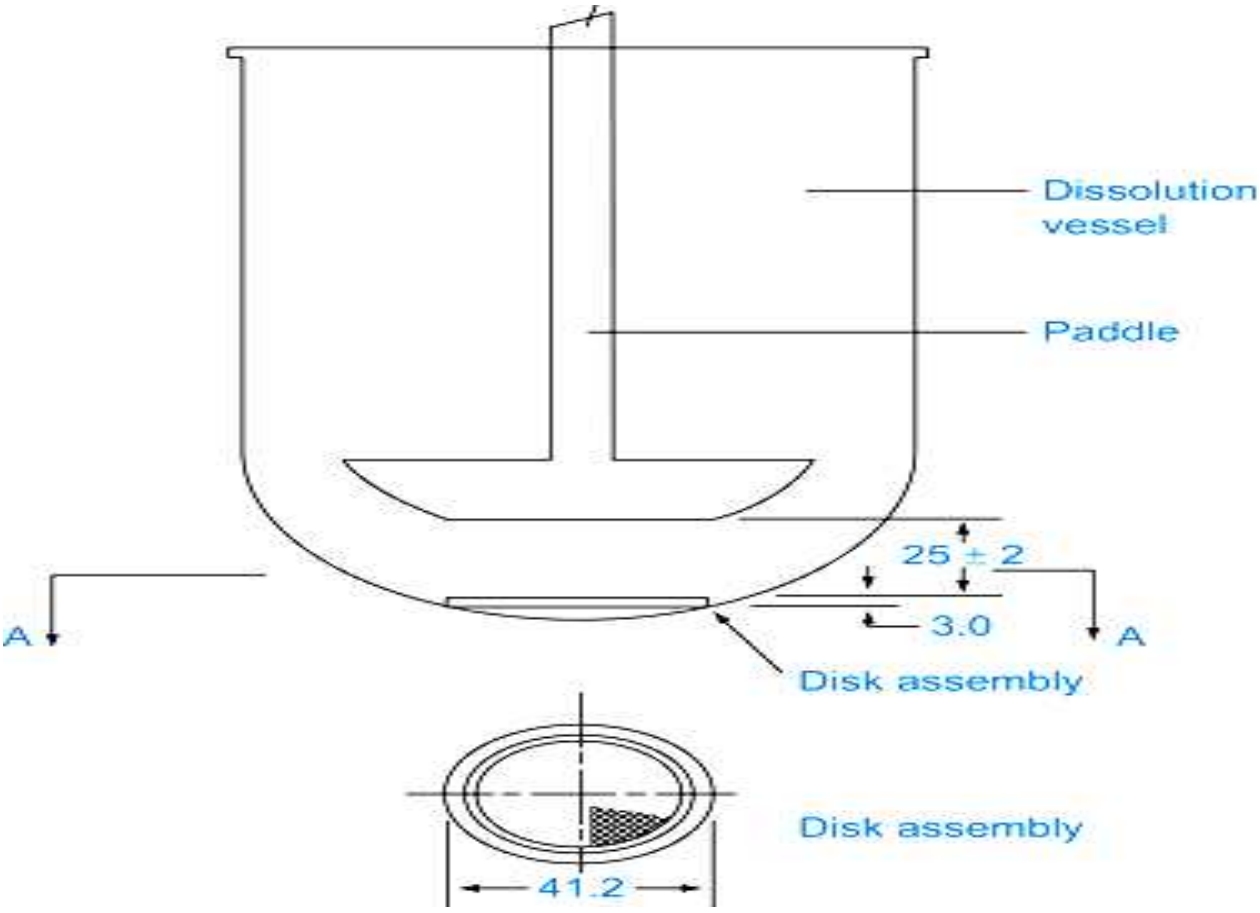

FIGURE 7: PADDLE OVER DISC

3. MATHEMATICAL MODELS

3.1 Zero order release kinetics
3.2 First order model
3.3 Higuchi model
3.4 Hixon crowell model
3.5 Korsmeyer Peppas model

TABLE II: KINETIC MODELING OF DRUG DELIVERY SYSTEMS

DRUG RELEASE MODEL	EQUATION	DRUG DELIVERY DEVICE	APPLICATIONS	GRAPH PLOT
Zero order	Q = Q0 + K0t Where Q is the amount of drug released Q0 is the initial amount of drug in solution K0 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 antidepressants8	%CDR vs time [8] (Fig. 8)
First order	log C=log CO-kt/2.303 where CO is the initial concentration of the drug C is the final concentration of the drug k is the constant t is time	For dosage forms containing water soluble drugs in porous matrix	In elimination and absorption of drugs	log% CDR of amount remainingvs time [13]. (Fig. 9)
Hixon Crowell	Q01/3-Qt1/3=kt Where Q01/3=initial amount of drug in the tablet Qt1/3=amount of drug released at time t k is constant t is time	Sustained release tablets	In cases where particle size and surface area changes	Cube root of amount remaining vs time (Fig. 10)
Higuchi model	Q=A√D(2C-CS)CSt Q is the amount of drug released in time t C is the initial drug concentration CS 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 vs √time
Korsmeyer peppas model	Mt/MO=ktn Mt/MO=fraction of drug released	Drug release from polymeric systems	Diffusional release from polymeric films	log %CDR vs log time [14,15,16]. (Fig. 11)

FIGURE 8: ZERO ORDER PLOT

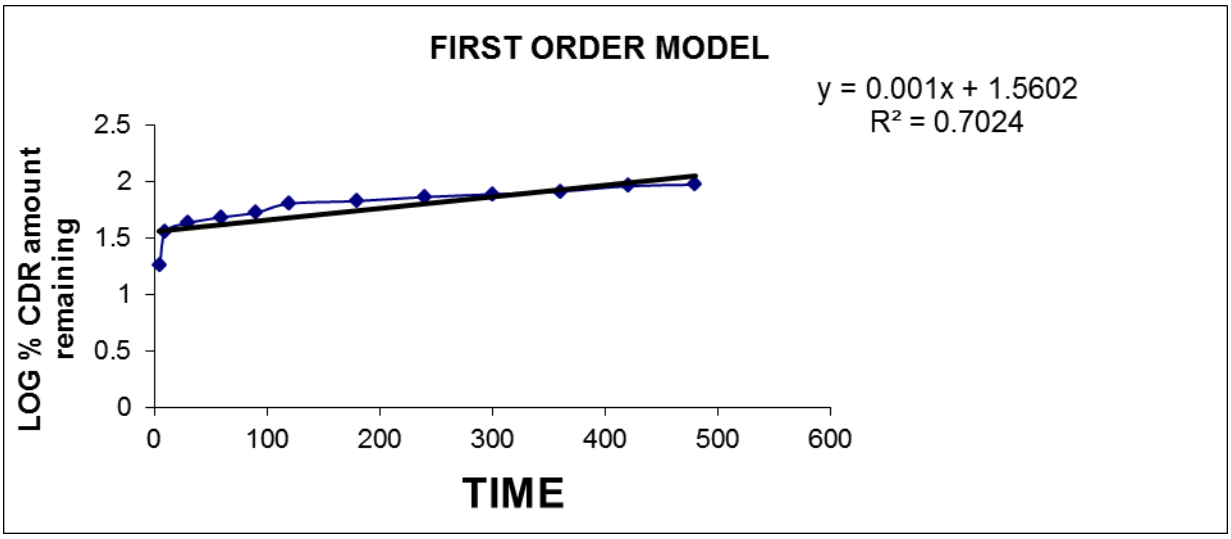

FIGURE 9: FIRST ORDER MODEL

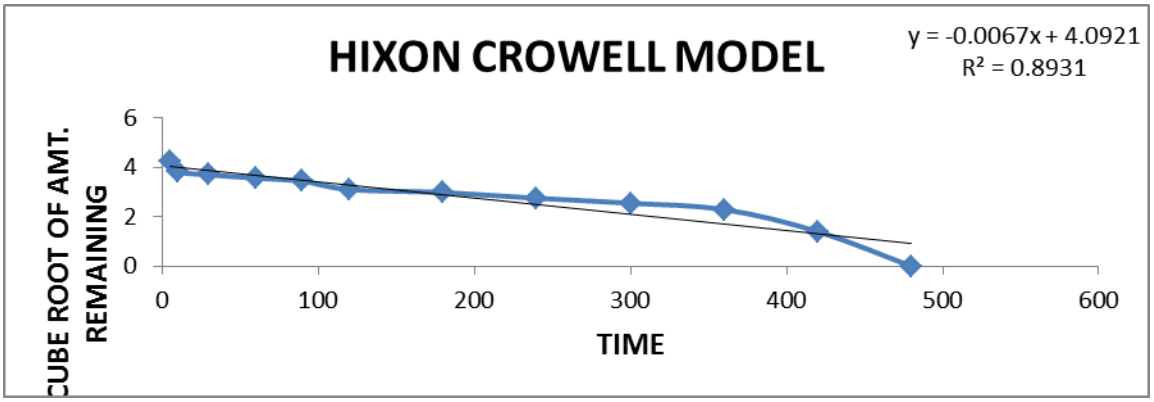

FIGURE 10:HIXON CROWELL MODEL

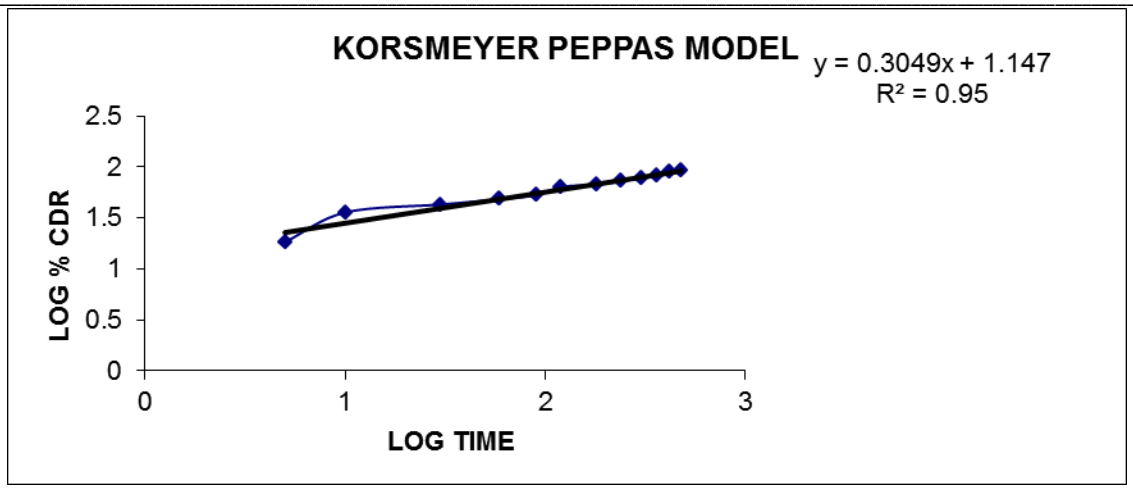

FIGURE 11: KORSMEYER PEPPAS MODEL

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.

References

1. Higuchi, W. I., Diffusional models useful in bio pharmaceutics drug release rate processes. J.Pharm. Sci., 1967, 56:315-324.
2. Essential of Medical Pharmacology,Jaypee brother medical publishers (P) KDT,2008; 196-197.
3. The United States Pharmacopoeia 27, NF 22, United States Pharmacopoeial Convention,Inc, 2004.
4. Collet J, Moreton C. Modified-release per oral dosage forms.In Aulton ME, ed. Pharmaceutics: Science of Dosage Form Design. United Kingdom: Churchill Livingstone 2002; 289-305.
5. Forbes Z, Magnetizable implants for targeted drug delivery (ONLINE) 2005[Cited may17];[2screens].Availablefrom:[URL:http//dspace.library.drexel.edu//retrieve/3657/Front.pdf]
6. Reddy, K. R.; Mutalik, S.; Reddy S. Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation andIn Vitro Evaluation. *AAPS PharmSciTech* 2003, *4* (4),480488.http://www.springerlink.com/content/7104416110g33lp7/fulltext.pdf (accessed Jan 15, 2012).
7. Carrico, C.K.,Workshop report – AAPS:USP workshop on dissolution calibration and testing. Pharm. Res.1996;13, 6–9.
8. Varelas, C.G., Dixon, D.G., Steiner, C.,Zero-order release from biphasic polymer hydrogels. J. Control.Release 34, 1995, 185–192.
9. Kramer J,Lindauer RF,Siewert M,Stricker H,Blume Extended release theophylline alternative *in vitro* dissolution methods.European journal of Drug metabolism and pharmacokinetics.1993,18:37
10. El-Arini K,Shiu GK,Skelly JP.Theophylline release preparations and fatty food: An in vitro study using the rotating dialysis cell.Pharm. Res.1990; 7:1130-1140
11. Costa P,Sousa Lobo.Modelling and comparison of dissolution profiles. European journal of pharmaceutical scences.2001; 13:123-133
12. Cohen DS,Erneaux T.Free boundary problems in controlled release pharmaceuticals: diffusion in glassy polymers.SLAM. J. Appl. Math.1988; 48:1451-1465
13. Ahmed K.in vitro release kinetics study of Ambroxol hydrochloride pellets developed by extrusion spheronisation technique followed by acrylic polymer coating. Pharm.Sci.2001;13:123-133
14. Korsmeyer RW,Gurny R,Doelker E,Buri P and Peppas NA.Mechanisms of solute release from hydrophilic porous polymers.Int. J. Pharm.1983;15:25-35

15. Korsmeyer RW,Lustig SR,Peppas NA.solute and penetrant diffusion in swellable polymers.mathematical modeling. J.Poly. Sci. Poly.Phys. Ed. 1986;24:395-408
16. Korsmeyer RW,Von meerwall E,Peppas NA.solute and penetrant diffusion in swellable polymers,verification of theoretical models. J.Poly. Sci. Poly.Phys. Ed. 1986;24:409-434