Developing a sustained drug delivery system

ASSIGN BUSTER

1. INTRODUCTION

In last few years, Formulations that are able to extend the release of drug have become an integral part of Pharmaceutical research. It is a centre of exploration due to its many benefits over conventional dosage form.

Sustained drug delivery system was aimed to release the medication in a prolonged rate. The basic concept of the sustained release dosage form development is to reduce the frequency of dosage administration, to reduce the fluctuations of drug in the plasma by maintain plasma drug level [1] thus improves.

Various expressions such as sustained-release , controlled-release, prolonged-action and repeat action have also been used to describe.. Sustained release offers prolonged delivery of drugs and maintenain plasma levels within a therapeutic range, steady-state plasma levels can be maintained without oscillation [2 , 3] . The sustained level of the medication was obtained by controlling the plasma blood level and less frequent dosing [4] (Lachman et al., 1987).

1. 1Matrix system isclassified into 5 typesbased on Hydrophilic Matrix System and insoluble hydrophobic Inert Matrix system [(6-8)]

1. 1. 1Hydrophobic Matrix tablet

In this technique of sustained release from an oral dosage form the drug is mixed with an inert or hydrophobic polymer and then compressed into a tablet. The sustained release is obtained by dissolving drug and was diffused

through a network of channels that exist between compacted polymer particles. The materials used as inert or hydrophobic matrices consist of polyvinyl chloride, polyethylene, and ethyl cellulose and ammonia methacrylate copolymers.

The rate controlling phase in these formulations is the solvent penetration into the matrix. The possible mechanism of drug release in the hydrophobic matrix tablet was by diffusion. Hydrophobic matrix tablet consist of porous and nonporous matrix systems.

1. 1. 2Hydrophilic matrix tablets

The drug molecules are combined with the polymer and erode slowly in body fluids. Hydroxy propyl methyl cellulose is commonly used polymer in the hydrophilic matrix tablets. It is a simple method and widely accepted due to its desirable global regulatory acceptance, cost effective, flexibility in drug release profile matching and ease of commercial scale-up.

The different grades of Hydroxypropylmethylcellulose were available for the design of sustained drug delivery system. The viscosity range of the Hydroxypropyl methylcellulose assist in the percentage release rate of drug release. The low viscosity range polymer cause increase in the drug release. The hydrophilic matrix system the mechanism of drug release occurs mainly by diffusion and erosion.

In the hydrophilic matrix system the use of cellulosic polymer cause gel formation on the surface of polymer and cause tablet erosion with

continuous release of drug. The polymers commonly used in the hydrophilic matrixes are classified into three categories.

Cellulose derivatives- hydroxyethylcellulose, Methylcellulose, Hydroxy propylmethylcellulose grades like K4M, K100M, 5cPs, 15cPs and Sodium carboxymethylcellulose. Semi synthetic polymers- Modified starches, Alginates and Chitosan. Acrylic acid Polymers -Carbopol 934

1. 1. 3. Wax matrix tablets

The drugs are embedded into lipid matrix by spray congealing in air and Wax-matrix tablet core consisting of semi-synthetic glycerides and blend congealing in an aqueous media. The congealing process use with or without the aid of surfactants, the wax matrix components are prepared from the blend of powdered ingredients.

1. 1. 4. Gum type matrix tablets

In this type of matrix system the excipients produce gel like consistency in presence of water and the dispersion of the active drug of the tablet was maintained by gel barrier. For example xanthan gum and sodium alginate in water soluble polysaccharides used in gum type matrix systems.

appropriate method depends on the properties of the drug, polymer and selection of other ingredients.

Many statistical experiments are useful tool to develop sustained release formulation with an optimized formulation with an appropriate dissolution rate with a minimum number of trials. For this reason, a computer based

optimization technique with a response surface methodology (RSM) utilizing a polynomial equation and artificial neural network (ANN) has been widely used (Ghosh et al., 2008andBozic et al., 1997).

2. 0KINETICS OF DRUG RELEASE

Various mathematical models utilized to interpret the mechanism of the drug release from ER dosage form, with the available dissolution data these release kinetics can be calculated using the model that best fit is selected based on the correlation coefficient (r) value in various models, which gives higher ‘ r’ value is considered as the best fit of the release data. The following are the various Release kinetics

- Cumulative percentage drug released Vs time (In-Vitro drug release plots)
- Cumulative percentage drug released Vs Square root of time (Higuchi’s plots)
- Log cumulative percentage drug remaining Vs Time (First order plots)
- Log cumulative percentage drug released Vs log time (Peppas plots)
- Calculated regression coefficients for zero order, first order, Higuchi and Korsmeyer-Peppas. The best fit model with the highest correlation coefficient.

Table No. 3. Analysis of diffusion release mechanisms

Release exponent (n)	Overall solute diffusion mechanis

	m
0. 5	Fickian diffusion
0. 5 < n < 1	Non-Fickian diffusion
1. 0	Case II transport
n > 1. 0	Super Case II transport

Zero order release is calculated from the following equation Qt = Q_0 + K_0 t where Q_0 = initial amount of drug Qt = cumulative amount of drug release at time “ t” K_0 = zero order release constant t = time in hours It describes the systems where the drug release rate is independent of its concentration of the dissolved substance.

The first order release equation is calculated from the following equation Log Qt = Log Q_0 + Kt /2. 303 where Q_0 = initial amount of drug Qt = cumulative amount of drug release at time “ t” K = first order release constant t = time in hours Here, the drug release rate depends on its concentration

The Hixson – Crowell release is calculated from the following equation is Where Q_0 = Initial amount of drug Qt = Cumulative amount of drug release

at time “ t” KHC = Hixson crowell release constant t = Time in hours. It describes the drug releases by dissolution and with the changes in surface area and diameter of the particles or tablets

A linear plot of the cube root of the initial concentration minus the cube root of percent remaining versus time in hours for the dissolution data in accordance with the Hixson-crowell equation.

The Higuchi release is calculated from the following equation

Q= KHt $_{1/2}$ where Q = cumulative amount of drug release at time “ t” KH = Higuchi constant t = time in hours The Higuchi equation suggests that the drug release by diffusion. A graph is plotted between the square root of time taken on x-axis and the cumulative percentage of drug release on y-axis and it gives a straight line.

Korsmeyer – peppas equation is F = (Mt /M) = Kmtn Where F = Fraction of drug released at time ‘ t’ Mt = Amount of drug released at time ‘ t’ M = Total amount of drug in dosage form Km = Kinetic constant n = Diffusion or release exponent t = Time in hours

An optimal experimental formulation was compared with the original product, in order to compare the profile of the in vitro release of the drug.

3. 0BIOAVAILABILITY STUDY:

Stabilitytesting of Drug products conducted as per ICH conditions the formulations which are stable up to 6M 40°C/75% RH and 25°C/60% considered as stable formula taken up for *in vivo* absorption study.

In current scenario *in vitro* and *in vivo* performance of the dosage forms is essential part of Product development. The FDA guidelines respecting the IVIVC method evaluation used to set dissolution specifications; which can be applied for surrogate for *in vivo* bioequivalence for certain pre- or post approval changes, such as Equipment, facility or Manufacturing process changes and minimizes the bioavailability or bioequivalence study after the formulation design optimization

The ultimate aim of IVIVC is to select the suitable dissolution method of in vivo absorption of the test compound.

In IR tablets the release is more rapid in ER, the excipients also having bio pharmaceutical activity and controls the release within the body. Generally HPMC matrices are biocompatible and do not have enzyme degradation by gastric fluids.

For Biovailability study the following Pharmacokinetic parameters to be studied they are Tmax, Cmax and AUC can be evaluated via Plasma or Urine data.

Pharmacokinetic assessment the plasma drug concentrations determined by HPLC analysis. Drug extracted from plasma sample by liquid-liquid extraction method, To study the rate and extent of absorption of Cilostazol and Etodolac extended release matrix tablets 100 with that of 100 mg reference(R) conventional marketed formulations and IR tablets

The research study was performed in rabbit model to evaluate the pharmacokinetics and then for IVIVC studies. The simple HPLC method used

to evaluate to determine the drug content in plasma, the in-vitro studies shows the release pattern is slow first order, For Cilostazol the overall Cmax, Tmax, AUC0-t, Kel and T1/2 were completely different between both test and reference formulation (IR). Therefore the prepared formulation was releasing the drug for a prolonged period of time

In case of Etodolac the Cmax, Tmax, AUC0-t, Kel and T1/2 were completely comparable with the reference product; therefore the prepared formulation was releasing the drug for a prolonged period of time and bioequivalent with reference product.