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SUSTAINED RELEASE SOLID DOASGE FORM: CONCEPT AND FORMULATION DESIGN NECCESITIES

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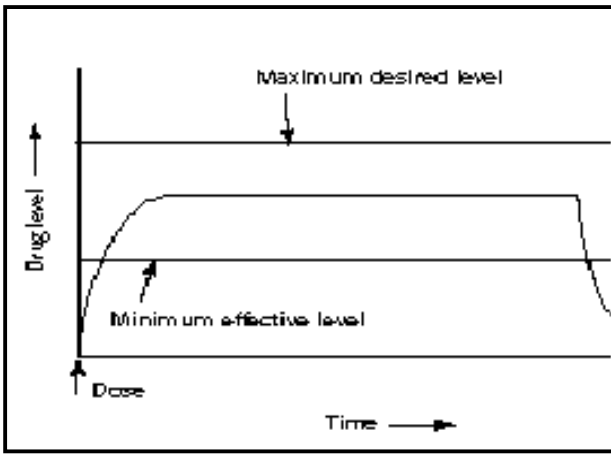
Abstract

Oral Sustained release (SR) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamic properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance. Developing oral sustained release matrix tablets for drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion. Highly water soluble drugs like Diltiazem; Ranitidine has been formulated as sustained release matrix tablets. This article contains the basic information regarding design sustained-release formulation and also the different types of the same

INTRODUCTION

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in Figure.[1]



(Drug levels in the blood with Controlled drug delivery systems)

The ideal object of drug delivery system points to the two aspects, most namely spatial placement and temporal delivery of drug. Spatial placement release to targeting of a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An approximately designed sustained release drug delivery system can be a major advance toward solving those two problems. It is for their reason that the science and technology responsible for development of SR pharmaceuticals have been and continue to be focus of a great deal of attention in both industrial and academic laboratories. The fact that coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement is a compelling matter for investigation of SR drug delivery system.

Simple definition of sustained release drug system is **"that achieves slow release of drug over extended period of time not particularly at a pre-determine rate.**

In any case, the scientific framework required for the successful development oral sustained release drug delivery system consist following three aspects.,

1. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.

2. The anatomic and the physiologic characteristics of the GIT.
3. Physicochemical characteristics and drug delivery mode of the dosage form to be designed.

The Goal In Designing Sustained Or Controlled Delivery System Is To:

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of novel drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery system. There are several reasons for the attractiveness of these dosage forms. The effectiveness of these drugs however is often limited by side effects or the necessity to administer the compound in a clinical setting.

The major goal set in designing sustained or controlled delivery is to:

- Reduce the frequency of dosing.
- Increase effectiveness of the drug by localization at the site of action.
- Reducing the dose required.
- Providing the uniform drug delivery.

Modified-Release Delivery Systems May Be Divided In To Four Categories:

A. Delayed release

B. Sustained release

1. Controlled release
2. Extended release

C. Site specific targeting

D. Receptor targeting

➢ **Delayed release:**

Delayed-release dosage forms can be defined as systems which are formulated to release the active ingredient at a time other than immediately after administration. Delayed release from oral dosage forms can control where the drug is released, e.g. when the dosage form reaches the small intestine (enteric-coated dosage forms) or the colon (colon-specific dosage forms).

Delayed-release systems can be used to protect the drug from degradation in the low pH environment of the stomach or to protect the stomach from irritation by the drug. In these cases drug release should be delayed until the dosage form has reached

the small intestine often polymers are used to achieve this aim. The dosage form (for example, a tablet or the granules before tableting) can be coated with a suitable polymer. The polymer dissolves as a function of pH, so when the dosage forms travel from the low-pH environment of the stomach to the higher-pH environment of the small intestine, the polymer coat dissolves and the drug can be released. Once this occurs, the release is again immediate and the resulting plasma.

- **Extended release**

Extended-release systems allow for the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced. For immediate-release dosage forms the time interval the plasma concentration is in the therapeutic range of the drug can be quite short. Therefore frequent dosing, with its associated compliance problems, is required. This is especially an issue in chronic Diseases when patients need to take the medicine for prolonged periods of time, often for the rest of their life. Extended release can be achieved using sustained- or controlled-release dosage forms.

- **Sustained release**

These systems maintain the rate of drug release over a sustained period For example, if the release of the drug from the dosage form is sustained such that the release takes place throughout the entire gastrointestinal tract, one could reduce Cmax and prolong the time interval of drug concentration in the therapeutic range. This in turn may reduce the frequency of dosing, for example from three times a day to once a day. Sustained-release dosage forms achieve this mostly by the use of suitable polymers, which are used either to coat granules or tablets (reservoir systems) or to form a matrix in which the drug is dissolved or dispersed (matrix systems).

The release kinetics of the drug from these systems may differ:

Reservoir systems often follow a zero-order kinetics (linear release as a function of time). Matrix systems often follow a linear release as a function of the square root of time.

- **Controlled-release:**

Controlled-release systems also offer a sustained-release profile but, in contrast to sustained-release forms, controlled-release systems are designed to lead to predictably constant plasma concentrations, independently of the biological environment of the application site. This means that they are actually controlling the drug concentration in the body, not just the release of the drug from the dosage form, as is the case in a sustained-release system. Another difference between sustained- and controlled-release dosage forms is that the former are basically restricted to oral dosage forms whilst controlled-release systems are used in a variety of administration routes, including transdermal, oral and vaginal administration. Controlled release of drugs from a dosage form may be achieved by the use of so-called therapeutic systems. These are drug delivery systems in which the drug is released in a predetermined pattern over a fixed period of time. The release kinetics is usually zero-order. In contrast to sustained-release systems, the dose in the therapeutic systems is of less importance than the release rate from the therapeutic system. Ideally the release rate from the dosage form should be the rate-determining step for the absorption of the drug and in fact for the drug concentration in the plasma and target site. However, controlled-release systems are not necessarily target-specific, which means that they do not 'exclusively deliver the drug to the target organ. This may be achieved by so-called targeted delivery systems which aim to exploit the characteristics of the drug carrier and the drug target to control the bio distribution of the drug.

- **Targeted-release dosage forms:**

Whilst controlling the rate of release of a drug from its delivery system can control plasma drug concentration levels, once released there is often little control over the distribution of the drug in the body. Very few drugs bind exclusively to the desired therapeutic target and this can give rise to reduced efficacy and increased toxicity. Drug targeting aims to control the distribution of a drug within the body such that the majority of the dose selectively interacts with the target tissue at a cellular or sub cellular level. By doing so, it is possible to enhance the activity and

specificity of the drug and to reduce its toxicity and side-effects. Drug targeting can be achieved by designing systems that passively target sites by exploiting the

natural conditions of the target organ or tissue to direct the drug to the target site. Alternatively drugs and certain delivery systems can be actively targeted using targeting groups such as antibodies to bind to specific receptors on cells.

Principle of Release Rate and Dose Consideration:

The objective in designing a sustain release system is to deliver drug at a rate necessary to achieve and maintain a constant drug level. This rate should be analogous to that achieved by continuous IV infusion where drug is provided at a constant rate equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time that is release from the dosage form should follow zero order kinetics. Shown by following equation.

kr^0 = Rate In = Rate out = ke. Cd. Vd

Where

kr^0 – Zero order rate constant for drug release.

Ke - First order rate constant for overall drug elimination.

Cd - Desirable drug level in the body.

Vd - Volume space in which drug is distributed/volume of distribution.

To achieve a therapeutic level promptly and sustaining the level for a given period of time, the dosage form generally consists of two parts, an initial priming dose, Di, that release drug immediately and a maintenance or sustaining dose, Dm. The total dose, W, thus required for the system is –

$W = Di + Dm$ (1)

For a system where the maintenance dose release drug by a zero order process for a specified period of time, the total dose is

$W = Di + Kr^0\ Td$ (2)

Where Kr^0 is the zero order rates constant and Td is the total time desired for sustained release form and dose.

Advantages of Sustained Release Products:

1. Decreased local and systemic side effects

- Reduced gastrointestinal irritation.

2. Better drug utilization:

- Minimum drug accumulation on chronic dosing.

3. Improved efficiency in the treatment

- More uniform blood concentration.
- Reduction in fluctuation in drug level and hence more uniform pharmacological response.

4. Improved patient compliance

- Less frequent dosing
- Reduced night-time dosing

5. Economy

- Although the initial unit cost of sustained release products is usually greater than that of the conventional dosage form because of the special nature of these products, the average cost of treatment over an extended time period may be less.

Challenges In The Development Of Sustained Release Dosage Form:

a. Dose dumping:

Dose dumping is a phenomenon where by relatively large quantities of drug in a sustained release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index.

b. limited choice of selecting desired dose in the unit:

In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of sustained release dosage forms, this appears to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

c. Poor In Vitro – In Vivo correlation:

In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called 'Absorption window' becomes important and may give rise to unsatisfactory drug absorption in vivo

despite excellent in-vitro release characteristics

Criteria To Be Met By Drug Proposed To Be Formulated In Sustained Release Dosage Forms:

❖ **Desirable half-life:**

The half life of a drug is an index of its residence time in the body. If the drug has a short half life (less than 2 hours), the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from, and sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half- life of three to four hours.

❖ **High therapeutic index:**

Drugs with low therapeutic index are unsuitable for incorporation in sustained release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities

❖ **Small dose:**

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for sustained release is seriously undetermined. This is chiefly because the size of a unit dose sustained release formulation would become too big, to administer without difficulty.

❖ **Desirable absorption and solubility characteristics:**

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into sustained release formulations is therefore unrealistic and may reduce overall absorption efficiency.

❖ **Desirable absorption window:**

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the 'absorption window'. Drugs exhibiting an absorption window

❖ **First pass clearance:**

As discussed earlier in disadvantages of sustained delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive. hepatic first pass

metabolism, when administered in sustained release forms.

Sustained Release Formulation Design

Sustained (Zero-order) drug release has been attempted to be achieved by following classes of sustained drug delivery system.

1. Dissolution-sustained release system

a. Encapsulation dissolution control

b. Matrix dissolution control

2. Diffusion-sustained release system

a. Reservoir devices

b. Matrix devices

3. Methods using lon Exchange

4. Methods using Osmotic pressure

5. pH– Independent formulations

6. Altered density formulations.

1. Diffusion sustained system:

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount / area -time), across a membrane in the direction of decreasing concentration is given by Fick's law.

J= - D dc/dx.

D = diffusion coefficient in area/ time

dc/dx = change of concentration 'c' with distance 'x'

In common form, when a water insoluble membrane encloses a core of drug, it must diffuse through the membrane, the drug release rate dm/ dt is given by

dm/ dt= ADK C/L

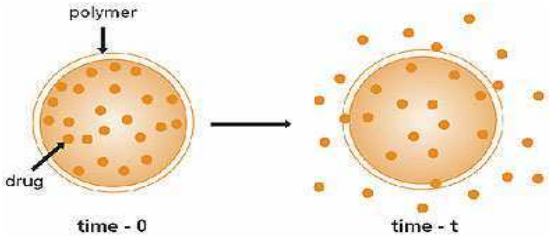
Where A = area

K = Partition coefficient of drug between the membrane and drug core

L= diffusion path length [i.e. thickness of coat]

c= concentration difference across the membrane.

A. Reservoir type:



(Schematic representation of diffusion sustained drug release: reservoir system)

In the system, a water insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media Characterization

Advantages: Zero order delivery is possible, release rates variable with polymer type.

Disadvantages: System must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if system fails.

B. Matrix type:

A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.

Higuchi has derived the appropriate equation for drug release for this system

Q = D□□/ T [2 A –□□ Cs] Cst½

Where;

Q = weight in gms of drug released per unit area of surface at time t

D = Diffusion coefficient of drug in the release medium

= porosity of the matrix.

Cs = solubility of drug in release medium

T= Tortuosity of the matrix

A = concentration of drug in the tablet, as gm/ ml

Advantages: Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds

Disadvantages: Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.

Thus diffusion sustained products are based on two approaches the first approach entails placement of the drug in an

insoluble matrix of some sort. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The second approach involves enclosing the drug particle with a polymer coat. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of liquid into the surrounding fluid.

2. Dissolution sustained systems:

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the device until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

A. Reservoir type:

Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats as shown in figure, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals.

Although this is not a true sustained release system, the biological effects can be similar. An alternative method is to administer the drug as group of beads that have coating of different thickness. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating.

B. Matrix type:

The more common type of dissolution sustained dosage form as shown in figure. It can be either a drug impregnated sphere or

a drug impregnated tablet, which will be subjected to slow erosion.

Two types of dissolution- sustained pulsed delivery systems:

Single bead– type device with alternating drug and rate-controlling layer

Beads containing drug with differing thickness of dissolving coats.

3. Methods using Ion Exchange:

It is based on the formation of drug resin complex formed when a ionic solution is kept in contact with ionic resins. The drug from these complex gets exchanged in gastrointestinal tract and released with excess of Na and Cl present in gastrointestinal tract

Resin + - Drug - + Cl goes to resin + Cl + Drug-

Where x is cl conversely

These systems generally utilize resin compounds of water insoluble cross – linked polymer. They contain salt – forming functional group in repeating positions on the polymer chain. The rate of drug diffusion out of the resin is sustained by the area of diffusion, diffusional path length and rigidity of the resin which is function of the amount of cross linking agent used to prepare resins.

4. Methods using osmotic pressure:

A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating

5. pH– Independent formulations:

The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered sustained release

formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release e.g. propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility.

THE CONCEPT OF PREFORMULATION:

Almost all drugs are marketed as tablets, capsules or both. Prior to the development of the major dosage forms, it is essential that certain fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. This in formation decides many of the subsequent events and approaches in formation development. This first learning phase is known as pre-Formulation. It can be defined as an investigation of physical And chemical properties of new drug substance alone or in Combination with other excipient. Pre-formulation is also Phase of research & development process where research

scientist characterize physical, chemical and mechanical aspect of new drug under investigation in order to developed stable safe & effective dosage form Pre-formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system. Pre-formulation scientist must consider the following factors:

- The amount of drug available.
- The physicochemical properties of the drug already known.
- Therapeutic category and anticipated dose of compound.
- The nature of information, a formulation should have or would like to have.

Pre-formulation drug characterization in a structured Program:

UV Spectroscopy.

The first requirement of any pre-formulation study is the development of as

simple analytical method for quantitative estimation in subsequent steps. Most of drugs have aromatic rings and/or double bond as part of their structure and Absorb light in UV range, UV spectroscopy being fairly accurate and simple method is a performed estimation Technique at early pre-formulation stages. The absorption Co-efficient of the drug can be determined by the formula:

E=AF/X

Where, A= Absorbance

F= dilution factor

X=weight of drug (mg)

It is now possible to determine concentration of drug in any Solution by measuring absorbance.

C= AF/Emg/ml

Following studies are conducted as basic pre-formulation studies, Special studies are conducted depending on the type of Dosage form and the type of drug molecules.

- Solubility determination
- pKa determination
- Partition co-efficient
- Crystal properties and polymorphism
- Practical size, shape and surface area.
- Chemical stability profile.

1. Solubility Determination

The solubility of drug is an important physicochemical property because it effects the bioavailability of the drug , the Rate of drug resale in to dissolution medium and consequently, The therapeutic efficiency of the pharmaceutical product. The solubility of the molecules in various solvents is determined as a first step. This information is valuable is developing a formulation. Solubility is usually determined in variety of commonly used solvents and some oils if the molecule is lipophillic. The solubility of material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged until equilibrium achieved

Common solvents used for solubility determination are

Water, Polyethylene Glycols, Propylene Glycol, Glycerin, Sorbitol, Ethyl Alcohol, Methanol, Benzyl Alcohol, IsopropylAlcohol, Tweens, Polysorbates, CastorOil, Peanut Oil, Sesame Oil, Buffer at various pHs

The solubility should ideally be measured at two temperature.

1. 4°Ctoensurephysicalstabilityandentered shortterm storage and chemical stability unit more definitive data are available. The minimum density of water occurs at 4C.
2. 2. 37°Cto support biopharmaceutical evaluation.

2. pKa Determination

Determination of the dissociation content for a drug capable Of ionization within a ph rang of 1to10 is important since Solubility and consequently absorption .The Henderson– Hassesle bach equation provide s an estimate of the ionized And unionized durg concentration at a particular pH. For acidic compounds

pH= pKa +log(un-ionized drug])/[ionized drug])

3. Partition Coefficient

Partition Co efficient (oil/water)is a measure of a drug's Lipophilicity and an indication of it sability to cross cell membranes. It is defined as the ratio of unionized drug distributed between the organic and aqueous phases at equilibrium.

Po/w=(Coil/C water)equilibrium.

For series of compounds, the partition co efficient can provide An empiric handle in screening for some biologic properties. For drug delivery, the lipophilic/hydrophilic balance has been shown to be a contributing factor for the rate and extent Of drug absorption. Although partition co efficient data alone Does not provide understanding of invivo absorption, it does Provide a means of characterizing the lipophilic /hydrophilic Nature of the drug. Since biological membranes are lipoidal in nature. The rate of drug transfer for passively absorbed drugs is directly related to the lipophilicity of the molecule. The partition coefficient is commonly determined using an oil phase of octanol or chloroform and water. Drugs having values if P much greater than1are classified as lipophilic, where as those with partition co

efficient much less than 1are indicative of a hydrophilic drug. Although it appears that the partition co efficient may be the best predictor of absorption rate, dissolution rate, pKa and solubility on absorption must not be neglected.

4. Melting Point

The melting point of a drug can be measured using three techniques

→ Capillary Melting

→ Hot Stage Microcopy

→ Differential scanning calorinetry or Thermal Analysis.

Capillary Melting

Capillary melting gives information about the melting range but it is different to assign an accurate melting point.

Hot Stage Microcopy

This the issued observation of melting under a microscope Equipped with a heated and lagged sample stage. The heating rate is controllable and up to three transitions can registered.

Differential Scanning Calorimeltry and thermal analysis

Differential thermal analysis (DTA) measures the Temperature difference between the sample and a reference as A function of temperature or time when heating at a constant Rate differential scanning calorinetry(DSC) is similar to DTA Except that the instrument measures the amount of energy Required to keep the sample at the same temperature as the Reference i.e. it measures the enthalpy of transition.

5. Crystal Properties and Polymorphism

Much drug substance can exit in more than one crystalline from with different pace lattice arrangements. This property is known as polymorphism. Polymorphs generally have different melting points, x-ray diffraction patterns and solubility even though they are chemically identical. Differences in the dissolution rates and solubility's of different polymorphic forms of a given drug are very commonly observed. When the absorption of a drug is dissolution rate limited, a more soluble and faster-dissolving from may be utilized to improve the rate and extent of bioavailability. For drugs pane to degradation in the solid state, physical form

of the drug influences degradation. Selection of a polymorph that is chemically more stable is a Solution in many cases. Different polymorph also leads to Different morphology, tensile strength hand density of power Bed which all contributes of compression characteristics of materials. Some investigation of polymorphism and crystal habit of a drug substance as it relates to pharmaceutical processing is desirable during its Preformulation evaluation especially when the active ingredient is expected to constitute the bulk of the tablet mass. Although a drug substance may exist in two or more polymorphic forms, only one form is thermodynamically stable at a given temperature and pressure. The other forms would convert to the stable form with time. In general, the stable polymorph exhibits the highest melting point, the lowest solubility and the maximum chemical stability. Various techniques are available for the investigation of the solid state. These include microscopy infrared spectrophotometry, single-crystal x-ray and x-ray power diffraction, thermal analysis.

6. **Particle Size, Shape and Surface Area**

Bulk flow, formulation homogeneity, and surface-area controlled processes such as dissolution and Surface Morphology of the drug particles. In general each new drug Candidate should be tested during Preformulation with the smallest particle size as is practical to facilitate preparation of Homogeneous samples and maximize the drug's surface area for interactions. Various chemical and physical properties of Drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also, in some instances, on their

→ **Particle size Determination:**

Though microscopy is the simplest technique of estimating size ranges and shapes, it is to slow for quantitative

Determination the material is best observed as a suspension in Non dissolving fluid. And reason Pipette is based on the rate difference of sedimentation of Different particles, but techniques like this are seldom used due to their tedious nature instruments based on light scattering,(Royco), light blockage(HIAC)and blockage of electrical conductivity path (coulter counter) are available.

→ **Surface Area Determination**

Surface area is most commonly determined based on brunavere metteteller(BET) theory of adsorption. Most

Substances adsorb a monomolecular layer of gas under Certain conditions of partial pressure of gas and temperature. Knowing the mono layer capacity of adsorbent and the area of Absorbale molecule, the surface area can be calculated the Adsorption process is carried out with nitrogen at-195°degree at a partial pressure attainable when nitrogen is in a 30%temperature with an inert gas (helium).The adsorption Takes place by virtue of vander wall's forces.

7. **Powder Flow Properties**

When limited amounts of drugs are available Powder flow Properties can be evaluated by measurements of bulk density and angle of repose. Changes in particles size, and shape are Generally very important an increase in crystal size or a more Uniform shape will lead to a small angle of repose and a Smaller Carr's index.

Bulk Density

Knowledge of absolute and bulk density of the drug Substance is Very useful in Having some idea as to the size Off in al dosage form the density of solids also of affects their Flow Properties Carr's compressibility index can be used to Predict the flow properties based on density measurement.

Carr's index = Tapped density - Bulk density / Tapped density X 100

A similar index has been defined by Hausner:

Hausner's ratio = Tapped density / Bulk density

Angle of repose

The maximum angle which is formed b/w the surface of a Pile of powder and horizontal surface is called the angle of repose.

8. **Compatibility studies**

The knowledge of drug excipients interaction is useful for the Formulation to select appropriate excipients. The described pre-formulation screening of drug excipients interaction requires only5mg of drug in a 50% mixture with the excipients to maximize an interaction. Mixtures should be examined under nitrogen to ultimate oxidation and paralytic effect at a standard

heating rate on DSC, over a temperature range, which will encompass any thermal changes due to both the drug and appearance or disappearance one or more peak sin thermogrames of drug excipient mixtures are considered of indicate on of interaction.

CONCLUSION

Development of sustained release oral dosage forms is beneficial for optimal therapy regarding efficacy, safety and patient compliance. In case of sustained release (SR) dosage forms the release of the active agent, although, is lower than in the conventional formulations, however, it is still substantially affected by the external environments into which it is going to be released. Sustained-release tablets are formulated so that the active ingredient is embedded in a matrix of insoluble substance (various: some acrylics, even chitin, these are often patented) so that the dissolving drug has to find its way out through the holes in the matrix. In some SR formulations the matrix physically swells up to form a gel, so that the drug has first to dissolve in matrix and then exit through the outer surface. Difference between controlled release and sustain release or sustained release is that controlled release is perfectly zero order release that is, the drug releases with time irrespective of concentration. On the other hand, sustain release or sustained release implies slow release of the drug over a time period. It may or may not be controlled release.

Pre-formulation studies have a significant part to play in Anticipating formulation problems and identifying logical Path in both liquid and solid dosage form technology. The Need for adequate drug solubility cannot be overemphasized. In parallel solid-state stability by DSC, TLC and HPLC in the Presence of tablet and capsule excipient will indicate the most Acceptable vehicles for solid dosage form. By comparing the physic chemical properties of each drug Candidate within a therapeutic group, the pre-formulation Scientist can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response and advise the bulk chemist about the selection and production of the best salt with appropriate particle size and morphology for subsequent processing.

REFERENCE

1. Brannon PL: L. Med. Plast. & Biomater, Med. Plast. & Biomater; 1998; 199(6): 34-46.

2. K.P. Sampath kumar, Debjit Bhowmik, Shweta Srivastava, Shravan Paswan and A.S. Dutta: Sustained Release Drug Delivery System Potential, The Pharma Innovation., 2012; 1(2): 48-60.

3. Chien YW: Novel drug delivery systems. 2nd ed. New York: Marcel Dekker Inc; 1992.

4. Lachman L, Lieberman HA and Kanig JL: The theory and practice of industrial pharmacy. 3 rd ed. Bombay: Varghese Publishing House; 1987.

5. Remington: the Science and practice of pharmacy; Lippincott Williams & wilkins 20th edition; 2002; 903-914.

6. Gwen M Jantzen; Joseph R Robinson; Sustained, controlled and targeted Drug Delivery; Marcel dekker, 2nd edition; 1989; 29-32.

7. Gudsoorkar VR, Rambhau D. sustained release of drugs. The Eastern Pharmacist 1993; 36 (429): 17-22.

8. D. M. Brahmankar & Sunil B. Jaishwal, Controlled release medication chapter 15th in Biopharmaceutics and Pharmacokinetics – A Treatise, 1st edition, Vallabh Prakashan: 347-353.

9. Rane Manish, Parmar Jayesh, Siahboomi Ali Rajabi. Hydrophilic Matrices for Oral Extended Release Influence of Fillers on Drug Release from HPMC Matrices. Pharma Times. 2010; 42(4).

10. Baker R W and Heller J: Material selection for trans-dermal delivery systems; In Had graft J, Guys R H, editors. Transdermal Drug Delivery: Development Issues and Research Initiatives. New York, Marcel DekkerInc.1989; 293-311.

11. Bromberg L: Crosslinked poly ethylene glycol networks as reservoirs for protein delivery, J Apply Poly Sci1996; 59; 459-466.