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FORMULATION & EVALUATION OF EXTENDED RELEASE TABLET

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INTRODUCTION

Extended release formulation is an important program for new drug research and development to meet several unmet clinical needs. There are several reasons for attractiveness of these dosage forms viz. provides increase bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, Reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. Extended release drug delivery system achieves a slow release of the drug over an extended period of time or the drug is absorbed over a longer period of time. [Gupta PK 1992].

Extended release (ER) dosage form is one of the drug products categorized under the term modified release dosage forms (FDA, 1997). It refers to products, which are formulated to make the drug available over an extended period after ingestion; thus, it allows a reduction in dosing frequency compared to a conventional type i.e. immediate release (IR) dosage form. Extended Release solid oral dosage forms can be classified into two broad groups: (i) single unit dosage forms (e.g. tablets) and (ii) multiple unit dosage forms or multiparticulate pellet systems. The systems can be further subdivided into two concepts regarding to the design of dosage forms: (i) matrix systems and (ii) reservoir systems.[Lecomte, F. 2004].

1. SINGLE UNIT DOSAGE FORMS

1.1 Matrix systems

Matrix or monolithic devices consist of drug dispersed homogenously throughout a continuous phase of polymer or lipid. The devices can be prepared either by the compression of a polymer/drug mixture or by the dissolution or melting, resulted in the molecularly dispersed drug. The drug transport often results from a combination of several mechanisms included dissolution, diffusion, swelling and erosion.

a. Water-soluble matrix formers

Water-soluble or hydrophilic matrices are a well known type of Extended release oral dosage forms. While hydroxypropyl methylcellulose (HPMC) is the most important hydrophilic carrier material, several others are also available; including (i) cellulose derivatives: hydroxypropyl cellulose (HPC), carboxymethylcellulose sodium (NaCMC), (ii) natural polymers: sodium alginate, carrageenan, chitosan and (iii) synthetic polymers: polymerized acrylic acid (Carbopol), polyvinyl alcohol (PVA), polyethylene oxide (PEO). It has been suggested, however, that the term ‘swellable matrices’ is more appropriate as it better explains the characteristic of the systems.

b. Water-insoluble matrix formers

Water-insoluble carrier materials include (i) lipid-base excipients: white wax, carnauba wax, glyceryl monostearate, hydrogenated vegetable oil, paraffin and (ii) polymer-based excipients: ethylcellulose (EC), cellulose acetate. In comparison to the hydrophilic matrices, the system has a greater physical stability, resulting in the less variable drug release and the lower incidence of ‘dose dumping’ in presence of food.

1.2 Reservoir systems

Reservoir systems are characterized by a drug-containing core surrounded by release-rate controlling polymer(s).

a. Coated tablets

An example of technology for Extended Release coated tablet is MODAS (Multiporous Oral Drug Absorption System;). The tablet core consists of the mixture of active drug and other excipients, subsequently coated with a solution of water-insoluble polymers and water-soluble excipients. Upon exposure to aqueous media, the surrounded coating is transformed into a semi-permeable membrane through which the drug diffuses in a rate-limiting manner.

b. Osmotic pump systems

Osmotic device is a special type of the reservoir systems, where the release rate of the drug is controlled dynamically by an incorporated osmotic agent in the active drug core. The rigid surrounding semi-permeable membrane consists for example of cellulose acetate. The drug is released through a defined, laser drilled delivery orifice in the membrane [Verma et al., 2002].

2 MULTIPARTICULATE PELLET SYSTEMS

2.1 Matrix systems

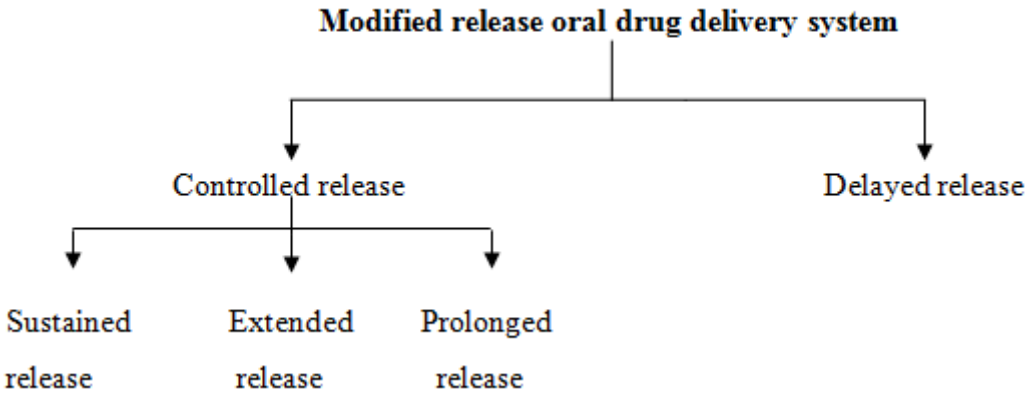
The matrix type of multiparticulate systems can be prepared by several techniques such as extrusion/spheronisation, spherical crystal agglomeration and melt-solidification. Although, the production of multiparticulate matrix systems is considered to be easier than that of the reservoir systems, their extent of retardation is limited because of pellet geometry.

2.2 Reservoir systems

Coated pellets as a mean to control drug delivery are widely used in the pharmaceutical industry, although the development and optimisation of the systems are rather complex.

There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drug delivery system, two pre-requisites would be required: Firstly single dose for the duration of treatment whether for days or weeks as with infection, diabetes or hypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects. [Verma, R.K., 2001]

There are certain considerations for the preparation of extended release formulations: If the active compound has a long half-life, it is sustained on its own, If the pharmacological activity of the active is not directly related to its blood levels, If the absorption of the drug involves an active transport and If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors need serious review prior to design. [Jantzen GM 1995]



The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. Extended release dosage form initially releases an adequate amount of drug to bring about the necessary blood concentration (loading dose, DL) for the desired therapeutic response and therefore, further amount of drug is released at a controlled rate (maintenance dose, DM) to maintain the said blood levels for some desirable period of time.

Objectives of Extended Release Drug Delivery System

Every novel drug delivery system had a rationale for developing the dosage form likewise, ERDDS also having some objectives that are discussed below.

Suitable Drug Candidate for Extended Release Drug Delivery System

The drugs that have to be formulated as a ERDDS should meet following parameters.

• It should be orally effective and stable in GIT medium.

• Drugs that have short half-life, ideally a drug with half life in the range of 2 – 4 hrs makes a good candidate for formulation into ER dosage forms eg. Captopril, Salbutamol sulphate.

• The dose of the drug should be less than 0.5g as the oral route is suitable for drugs given in dose as high as 1.g eg. Metronidazole.

• Therapeutic range of the drug must be high. A drug for Extended Release Drug Delivery System should have therapeutic range wide enough such that variations in the release do not result in concentration beyond the minimum toxic levels.

Drawbacks of Conventional Dosage Form [Wani MS 2008]

- Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

Advantages of Extended Release Delivery System [Hayashi T 2005]

- The extended release formulations reduce dosing frequency of drugs.
- The extended release formulations may maintain therapeutic concentrations.
- Reduce the toxicity by slowing drug absorption.
- The use of these formulations avoids the high blood concentration.
- Extended release formulations have the potential to improve the patient compliance and convenience.
- Minimize the local and systemic side effects.
- Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improve the bioavailability of some drugs.
- Usage of less total drug.
- Improve the ability to provide special effects.

For example, Morning relief of arthritis through bed time dosing.

Disadvantages of Extended Release Delivery System

Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.

- The larger size of extended release products may cause difficulties in ingestion or transit through gut.

- The release rates are affected by various factors such as food and the rate of transit through the gut.
- Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
- High cost of preparation.
- Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.

Rationale of Extended Drug Delivery. [Venkatraman S. 2000]

The main objective to formulate an API in an extended drug delivery system is related to its pharmacokinetics parameters. An appropriate formulation can make the absorption, distribution, metabolism and elimination (ADME) profile of a drug much more favourable.

This change of the ADME can have a profound impact on many aspects of the clinical use of the drug from patient compliance and convenience to its very efficacy, tolerance and safety parameter.

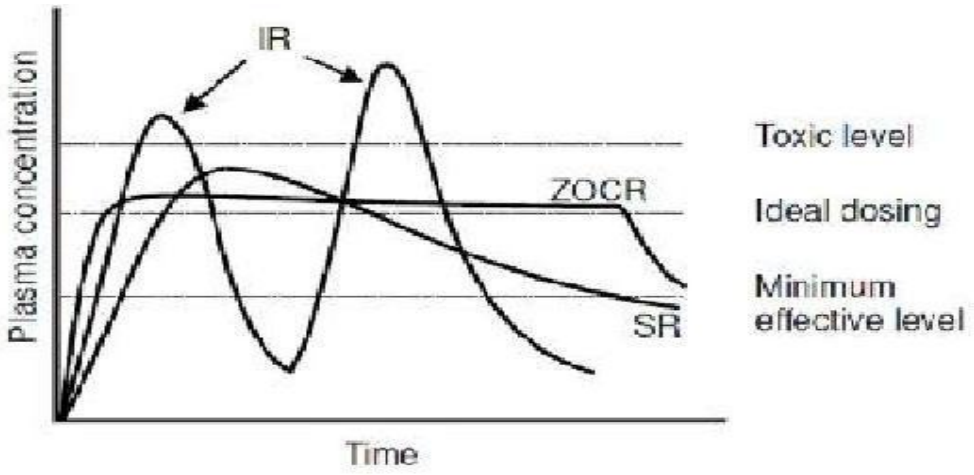


Figure: Plasma Concentrations.

Drug Properties of Extebded Release Formulations

During design of extended release delivery systems, variables such as the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug, are considered of particular interest to the scientist designing the system are the constraints imposed by the properties of the drug. These properties are classified as.

(a) Physicochemical

(b) Biological properties

These properties have the greatest effect on the behaviour of the drug in the delivery system and in the body. There is no clear cut distinction between these two categories since the biological properties of a drug are a function of its physicochemical properties. By definition, physicochemical properties are those that can be deter-mined from in vitro experiments and biological properties will be those that result from typical Pharmacokinetic studies of the absorption, distribution, metabolism, and excretion (ADME) characteristics of a drug and those resulting from pharmacological studies.[Patel P.2010]

Physicochemical Properties

a) Dose Size
b) Aqueous Solubility and pKa
c) Partition Coefficient
d) Drug Stability
e) Molecular Size and Diffusivity
f) Drug Protein Binding

Biological Properties

a) Absorption
b) Distribution
c) Metabolism
d) Elimination and Biological Half-Life

Evaluation Parameter of Extended Release Tablet

Physical Characterization of Granules

All physical tests of granules were performed like Bulk density, Tapped density, Compressibility index, Hausner's ratio and Loss on drying, sieve analysis.[Brahmankar HA 2000]

Tablet Evaluation

Prepared tablets were evaluated for certain physical properties like Tablet wt. variation, hardness, thickness, friability, dissolution study, Assay, etc.

1. Average Weight: 20 Tablets were taken randomly and weighed accurately and calculated the average weight of the tablets from each batch was calculated.

2. Hardness/ Crushing Strength: The term hardness indicates the ability of a Tablet to withstand mechanical shocks while handling. It is generally expressed in Kg/cm2 or in Newton (N). Hardness of an extended release tablet was measured using hardness testers.

3. Thickness: Three samples were selected randomly and thickness was measured using "Mitutoyo" Vernier caliper.

4. Friability: To achieve % friability within limits for a chewable tablet is a challenge to the formulator. Friability test is performed to assess the effect of friction and mechanical shocks, which may often cause Tablet to chip, cap, laminate or break.

METHOD

Samples of 20 Tablets were taken. Tablets were de-dusted prior to testing. Tablet samples were accurately weighed, and were placed in the drum of friability tester (Electrolab). Drum was rotated for 100 revolutions. Tablets were dedusted and reweighed.

$$\% F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

$W_{initial}$ – Initial weight of Tablets

W_{final} – Weight of Tablets after completing tests

5. Dissolution Test: This test provides evaluation of physiological availability of drug candidate. For FDA approval and bioequivalent product, it is important to compare the dissolution profile of product with the dissolution profile of Reference- Listed Drug. Therefore similarity factor (f2) is recommended by various regulatory committees that demonstrated the similarity in the percent (%) dissolution of test product with reference product. Dissolution profiles are considered similar if the calculated f2 value is between 50 and 100. The similarity factor (f) is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) difference of drug percent dissolved between the test and reference product. Dissolution tests were performed in a USP Dissolution Tester Apparatus I, II and III at 37 ± 0.5°C.

$$f_2 = 50 \cdot \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}$$

Literature Survey

1. Gavaskar B, Kumars SV, Sharan G, Rao YM. Prepared oral dissolving film technology (ODFTS) that can administrated in the buccal cavity for a shorter period of time (i.e., in seconds) and gives better therapeutic action. The methodologies used in the development of ODFTS for pediatric and geriatric patient's population, who are difficult in swallowing larger dosage forms, this technology has been used for local action, rapid release products. ODFT offers an alternate platform for molecules that undergoes first pass metabolism.[6]
2. Prasanthi N.L, Sowmya C, Krishna M, Gupta E. In this study sublingual fast dissolving films for an antiasthamatic drug, were prepared by solvent evaporation technique using different water soluble polymer. The Tween 80 is used as a solubilizing agent and an Aspartame is used as a sweetener. The prepared films were evaluated for thickness, uniformity in drug content, folding endurance, and disintegration time, swelling index, moisture loss, in-vitro drug release studies and drug-polymer compatibility studies. The results obtained showed that the prepared films were clear, transparent and smooth surface. Film containing hydroxyl propyl methylcellulose (2%w/w), Tween 80 (0.5%w/w) and Aspartame (0.5% w/w) showed optimum performance against all other prepared formulations.[7]
3. Mishra R and Avani A. In this study rapidly dissolving films of cetirizine hydrochloride were formulated by solvent casting method using pullulan as films forming polymer the prepared films were evaluated for the effect of type of casting surface and plasticizer as film separation and taste masking properties. The result revealed that the prepared films exhibited satisfactory thickness, tensile strength, percentage elongation and elastic modulas. In vitro dissolution studies and In vitro disintegration studies were found to be satisfactory.[8]
4. Manish Kumar, Garima G, Pushpendra Kumar, Kulkarni G.T. In this study buccal patch for systemic administration of famotidine in the oral cavity has been developed using hydroxy propyl methyl cellulose, sodium carboxy methylcellulose (SCMC) and polyvinyl alcohol by solvent casting method. The patches were evaluated for their physical characteristics like weight variation, thickness, drug content uniformity, surface pH, folding endurance, tensile strength, mucoadhesion strength, In vitro release studies were conducted for famotidine patches in phosphate buffer (pH, 6.6) solution. Patches exhibited drug release in the range of 72.58 to 91.91% in 20 min.[9]

5. Choudhury A, Sujoy Das, Dhangar S, Sumit K, Kanango A. In this study sustained release films of ciprofloxacin hydrochloride were formulated for the treatment of periodontal diseases. Films were formulated using different concentration of hydroxyl propyl methyl. cellulose and polyvinyl alcohol. The prepared films were subjected to different evaluation like determination of weight, thickness, surface pH, folding endurance, swelling index, mucoadhesion time, mucoadhesion strength, drug content, in vitro drug release study, ex-vivo release study and release kinetic behavior. From the results of evaluation it was concluded that all the prepared films having desire flexibility and mucoadhesive properties, along with that they shows good in-vitro and ex-vivo drug release performance. Drug release from the films follows desire sustained release phenomenon as needed in buccoadhesive drug delivery.[10]
6. Vijay kumar G, Ajay kumar P, Satish kumar P, Karunasri, Sri konda, Raghavender K and Priya P . In this study Montelukast sodium fast dissolving films were prepared by solvent casting method using HPMC as film base with different concentrations of super disintegrates like microcrystalline cellulose (MCC) and crospovidone using PEG400 as plasticizer. The Compatibility of the drug in the formulation was confirmed by IR and DSC studies. Scanning electron Microscopy revealed the morphology of the films. In vitro dissolution studies and mechanism of drug release was identified. The data demonstrated that 4% crospovidone and 10% MCC with 4% HPMC as a film base was suitable for developing fast dissolving films of Montelukast sodium.[1]

AIM

Formulation & Evaluation of Extended Release Tablets.

OBJECTIVE

a) To formulate extended release tablet by using different polymers.

b) To assess the effect of different polymers on release of drug from formulation.

c) To study the evaluation parameters of extended release tablet.

Plan of Work

1. Literature Survey
2. Selection of Drug and Excipients.
3. Procurement of Drug and Excipients.
4. Compatibility Study
5. Preformulation study of Drug

6. Evaluation of powder blend for

- Angle of repose
- Bulk density
- Carr's compressibility index
- Hausner's ratio

7. Formulation of Extended release tablets.

8. Evaluation of Extended release tablets

- Average Weight
- Hardness/ Crushing Strength
- Thickness
- Friability
- Dissolution Test

9. RESULT AND DISCUSSION

MATERIAL

Sr. No	**Ingredients**
1	Trazodone Hcl
2	Xanthum Gum
3	Acacia
4	Guar gum
5	Microcrystalline cellulose-102
6	Magnesium Stearate
7	Talc

Drug Profile of Trazodone Hydrochloride

- **Chemical Name:** 2-3-[4-(3-chloro)phenylpiperazin-1-yl]propyl-1,2,4trizole[4,3-a]pyridine-3(2H)-one hydrochloride.
- **Chemical Formula:** $C_{19}H_{22}ClN_5O$, HCl
- **Molecular Weight:** 408.3 g/mol.
- **BCS Class:** Class 1 High solubility high permeability
- **Half-Life:** 3-6 hours
- **Organoleptic Properties:** White, Crystalline powder.
- Trazodone hydrochloride is an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. Trazodone is used primarily in the treatment of mental depression or depression/anxiety disorders.

Method of Preparation

1.The extended release tablets of trazodone HCl were prepared by direct compression technique. For this trazodone HCl, xanthum gum and microcrystalline cellulose were passed through sieve #40.

2.All the above sifted ingredients were then mixed for 15 minutes.

3.Mag. Stearate and talc previously passed through sieve #60 was then mixed with above blend for 5 minutes.

4.The mixture(s) were then directly compressed in tablet punching machine with a 12 mm punch and die to obtain the tablet.

Formulation table.

Batches	Trazodone HCl	Xanthum gum	Guar gum	Acacia	MCC	Magnesium stearate	Talc
F1	100	100	----	----	244	3	3
F2	100	200	----	----	144	3	3
F3	100	300	----	----	44	3	3
F4	100	----	100	----	244	3	3
F5	100	----	200	----	144	3	3
F6	100	----	300	----	44	3	3
F7	100	----	----	100	244	3	3
F8	100	----	----	200	144	3	3
F9	100	----	----	300	44	3	3

Evaluation of Tablet

- Thickness(MM)
- Disintegration Time (sec)
- Hardness (kg/cm3)
- Friability test(%)
- Amount of drug content
- Weight variation
- Dissolution Time

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