FORMULATION AND EVALUATION OF ONDANSETRON HYDROCHLORIDE SUSTAINED RELEASE TABLETS

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Mr.M.Sakthivel, M.Pharm., Lecturer,
Department of Pharmaceutics,
Periyar College of Pharmaceutical Sciences for Girls,
Tiruchirapalli – 620 021.

CERTIFICATE

This is to certify that this dissertation entitled **"FORMULATION AND EVALUATION OF ONDANSETRON HYDROCHLORIDE SUSTAINED RELEASE TABLETS "** submitted by **Mr.M.SENTHIL VELAVAN** to The Tamilnadu Dr. M.G.R Medical University, Chennai in partial fulfillment for the award of the degree of "**MASTER OF PHARMACY"**in an independent bonafide work of the candidate carried out in the department of pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls, Tiruchirapalli–21, during the academic year 2007 -2008 under

my direct guidance and supervision and to my full satisfaction.

Place : Tiruchirapalli – 21

Date :

(**Mr.M.Sakthivel)**

Dr. R. Senthamarai, M.Pharm., Ph.D.,

Principal,

Periyar College of Pharmaceutical Sciences for Girls,

Tiruchirapalli– 620 021.

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guidance of **Mr.M.Sakthivel M.Pharm., Lecturer,** Department of Pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls, Tiruchirapalli – 21 during the academic year 2007 – 2008.

I recommend this research work for acceptance as project for the partial fulfillment for the degree of **"MASTER OF PHARMACY"** of the Department of pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls,Tiruchirapalli ,for the year September 2008.

Place : Tiruchirapalli – 21

Date :

(Dr. R. Senthamarai)

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Abbreviations

G.I.T.	-	Gastrointestinal Tract
Vs	-	Versus
App	-	Approximately
mg	-	Milligram
S.R.	-	Sustained Release
C.R.	-	Controlled Release
rpm	-	Revolution per minute
g	-	Gram
HPMC	-	Hydroxy Propyl Methyl Cellulose
IP	-	Indian Pharmacopoeia
ml	-	milliliter
m.m	-	millimeter
HPLC	-	High Performance Liquid Chromatography
R.T.	-	Room Temperature
Fig	-	Figure
USP	-	United States Pharmacopoeia

INTRODUCTION

1.1. SUSTAINED RELEASE DOSAGE FORMS[2,8,9]

Probably the earliest work in the area of sustained drug delivery forms can be traced to the 1938 patent of Israel Lipowski. There has been 60 years of research and development experience in the sustained drug release area since the patent, and a number of strategies have been developed to prolong drug level in the body. These ranges form the very simple slowly dissolving pellets or tablets to the more technologically sophisticated “controlled drug release systems” which have recently started to appear on the market and in the pharmaceutical literatures.

With many drugs, the basic goal of therapy is to achieve a steady-stage blood or tissue level that is therapeutically effective and nontoxic for an extended period of time. The design of proper dosage regimens in an important element in accomplishing this goal. In the recent past, controlled release concept and technology have received increasing attention in the face of growing awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional methods. Thus drug administered in the form of tablets, capsules, injectables and ointements etc., usually produce wide ranging fluctuations in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor as well as factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems or therapeutic systems. A dosage form that one or more drugs continuously in a pred pattern for a fixed period of time, either systemically or to a specified target organm is a controlled drug delivery system. The advent of drug delivery systems brings rate controlled delivery with fewer side effects, increased efficacy and

constant delivery. The primary objectives controlled drug delivery is to ensure safety of drugs as well as patient compliance.

Controlled release drug administration means not only prolonged duration of drug delivery, as in sustained released and prolonged released, but also implies predictability and reproducibility of drug release kinetics.

Description such as retard, slow, gradual, controlled, continuous, sustained, programmed, fractionated, deferred and pulsatile – release dosage forms and other similar definitions should be redefined as one of the following definitions.

Prolonged release dosage forms, that there may not be control of release rate, but prolong therapeutic blood or tissue level of the drug for an extend period of time. .

Delayed or repeated dosage forms that release the dose or a part (or parts) of the dose at a time (or times) different from that immediately following administration.

Oral sustained action products are of two kinds depending on the way in which the maintaining dose is released. For the so called repeat action and timed release products the maintaining does become available at discrete time intervals. If the maintain drug is continuously released, the product is of the prolonged action of sustained release type.

The goal of any drug delivery systems is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the

desired drug concentration. Two aspects are most important to drug delivery, namely, spatial pl acement and temporal delivery of a drug. Spatial placement related to targeting a drug to a specific organ or tissue. While temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed sustained-release drug delivery system can be a major advance towards solving these two problems.

The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug delivery. If one were to imagine the ideal drug delivery system, two perquisites would be required. First, it would be a single dose for the duration of treatment. Whether it be for days or weeks, as with infection, or for the lifetime of the patient, as in hypertension or diabetes. Second, it should delivery the active entity directly to the site of action, there by minimizing or eliminating side effects.

1.2 TERMINOLOGY[1,3,10]

There is considerable confusion in the terminology. The conventional dosage forms are immediate release types. Non-immediate delivery systems may be divided into three categories.

1. Delayed release
2. Sustained release
    a. Controlled release
    b. Prolonged release
3. Site-specific and receptor release

1. Delayed release

Delayed release systems are those that utilize repetitive, intermittent dosing of drug form one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules. A delayed release dosage form doses not product or maintaining drug blood levels with in the therapeutic range as shown in fig. 1

2. Sustained Release System

It includes any drug delivery system that achieves slow release of drug over an extended period of time.

a. Controlled release system

If the system is successful at maintaining constant drug levels in the blood or target tissue, it is considerable a Controlled release system.

b. Prolonged release system

If the system is unsuccessful at maintaining constant levels, the

duration of action is extended over that achieved by conventional delivery, it is considered a prolonged release system. This

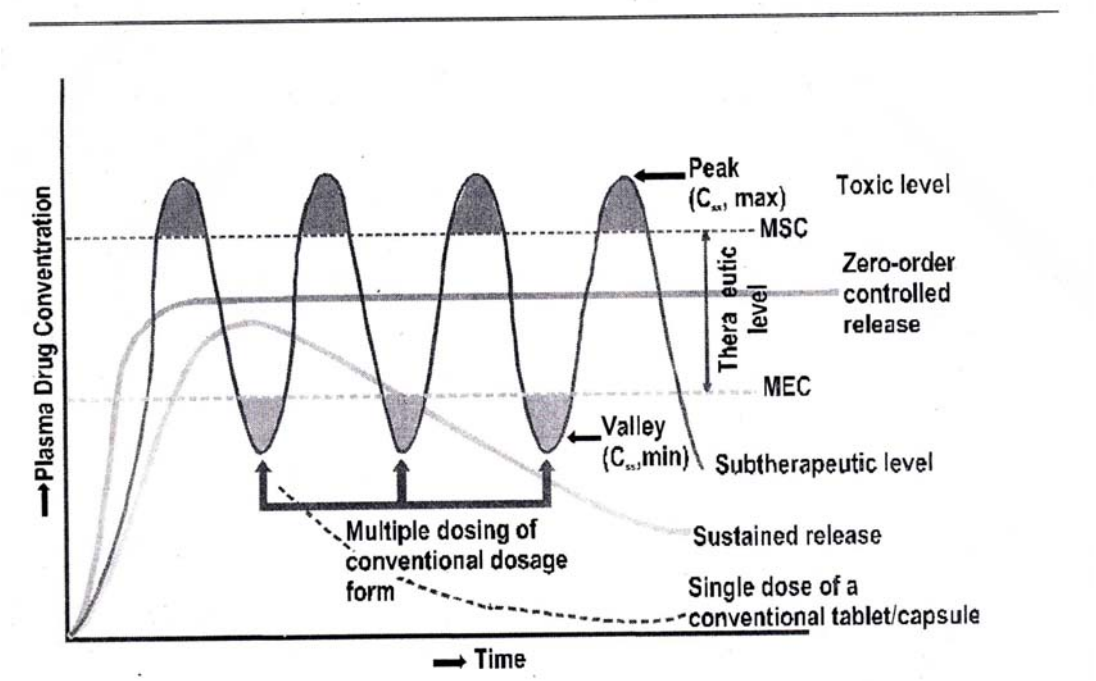


Fig.1.

Hypothetical plasma concentration – time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

3. Site Specific And Receptor Release

It refers to targeting of a drug directly to a certain biological location. In the case of site specific release, the target is a certain organ or tissue, while for Receptor Release the particular Receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery.

1.3. Requirements for sustained drug release[11,15,30]

Design of sustained release products is normally a very difficult task because of the interplay of the physical-chemical-biological properties of the drug, the patient disease state, and technological limitation in fabrication of the final dosage

form. Depending on the drug, disease state, route of administration, but a before a final decision is made to proceed with the dosage form, all the these factors must be considered.

(A) Release rate and dose calculation

The objective in designing a SR system is to deliver a drug at a rate necessary to achieve and maintain a constant drug blood level. The rate of delivery must be independent of the amount of the drug remaining in the dosage in the dosage form and constant over time. That is, release from the dosage form should follow zero- order kinetics as shown zero-order kinetics as shown by the following equation.

K_r = Rate In= Rate out = K_e. C_d.V_d

Where

K_r = Zero-order rate constant for drug release (among / time)

K_e = First – order rate constant for overall drug elimination (time-1)

C_d = desired drug level in the body (amount / Volume)

V_d = volume space in which the drug is distributed.

To achieve a therapeutic level promptly and sustain the level for a given period of time, the dose form generally consist of two parts.

$W = D_i + D_m$

Where,

W = the total dose

D_i = an initial priming dose

D_m = maintaining or sustaining dose.

(B) Drug properties

There are a number of physico-chemical and derived biological properties of the drug that either preclude placement of the drug in a sustained release system, or have an adverse influence on product design, making formulation of a SR system difficult, but not impossible. Thus b y changing the type of sustaining mechanism, the dose, or the route of administration; it might be possible to design a SR system.

1.4 Factors influencing the design of a SR dosage form [6,28,29]

1.4.1Physico-chemical properties

1.Dose

Drugs with a single oral dose larger than 0.5 gram are poor candidates for oral controlled products. A larger dose will generate a substantial volume depending on the density of the drug, duration of intended prolongation and mechanism of absorpti on. But the problem of large dose can be overcome by selecting an alternate route of drug administration.

2. **Aqueous solubility**

The aqueous solubility of a drug is an extremely important consideration in its incorporation into controlled release form. Extremes in aqueous solubility are undesirable in the preparation of controlled release products. Aqueous solubility exercises its control on the absorption process in two ways (a) by its influence on the dissolution rate and (b) by its ability to penetrate the tissues. Dissolution rate has limited the absorption of a variety of drugs. For e.g. griseofulvin, digoxin,

salicylamide, diazoxide and warfarin. A drug with aqueous solubility less than 0.01mg/ml is a poor candidate as a controlled release product since the drug is inherently sustained. For drug with low water solubility, it will be difficult to incorporate into a SR formulation.

The lower limit on solubility of such product has been reported to be 0.1 mg/ml hydrolysis or metabolism in the stomach and intestine is proportional to the residence time in these organs and the apparent rate constant for degradation. If the drug is in a solid form, only a small fraction of it will be in solution for possible degradation. Hence, it would appear possible to improve the apparent bioavailability of a drug which is unstable in the stomach by placing it in a slowly soluble or slowly available form. Since most controlled drug systems are designed to release their contents over much of the length of the gastro intestional tract, drugs which are unstable in the environment of intestine would be unusable to be formulated into such delivery systems. In addition to chemical degradation, metabolizing enzymes at the site of administration or along the pathway to the target area may also playa a significant role in drug availability.

5.Molecular size

Large molecules will show small diffusion coefficients and may be difficult to place into a suitable sustained release system. Drug of molecular weight up to 500-700 should present no difficulty in this regard.

The ability of a drug to diffuse through membrane, its so called diffusivity can be influenced by its molecular size as shown in equation.

Log D = - SV long V+ KV= -SM log M+KM

Where D is the diffusivity, M is molecular weight, V is molecular volume and SV, SM, KV, KM are constants. Molecular size of a drug is an important parameter that must be considered if a polymeric membrane is relied upon for the controlled release mechanism . The diffusion coefficient also plays a role in the ability of a drug to cross a biological membrane.

1.4.2 Biological Properties

1.Absorption

The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into sustained release system. Since the rate-limiting step in drug delivery from a sustained release system is release form the dosage forms rather than absorption, a rapid rate of absorption of the drug relative to its release is essential if the system is to be successful.

$$K_r \quad <<<< \quad K_a$$

This becomes most critical in the case of oral administration

Drug that are slowly absorbed or absorbed with a variable absorption rate are poor candidates for a SR system. For a oral dosage forms, the lower limit on the absorption rate constant is in the range of $0.25h^{-1}$ (assuming a GI transit time of 10-12hr).

To maintain a constant blood or tissue level of drug it must be uniformly release from the controlled release products and then uniformly absorbed. The fraction of drug absorbed from a conventional dosage form can sometimes be quite low for a variety of reasons, such as3. drug degradation due to metabolism, binding of drug to proteins and physical loss. Placement of labial drug in controlled drug delivery systems can sometimes improved the fraction of dose absorbed.

Drugs absorbed by specialized transport processes and drugs absorbed at special sites of the gastro intestinal tract are also poor candidates for real controlled release products. Drugs which are slowly absorbed are also not good for controlled release dosage forms primarily because drug availability is limited by gastro intestinal transit time.

2.Distribution

The design of sustained release systems usually based on only a few pharmacokinetic parameters one of which is the volume of distribution, expressed by following equation.

$$V = dose/C_0$$

Where,

Co= drug concentration immediately after an I.V. bolus injection but before any drug has been eliminated.

The distribution of a drug into vascular and extra-vascular spaces in the body is an important. factor in its overall elimination kinetics. His in turn sustained release system, primarily by restricting the magnitude of release rate and the dose size, which can be employed.

Drugs with high apparent volumes of distribution, which in turn influences the rate of elimination for the drug, are poor candidates.

3.Metabolism

The metabolic conversion of a drug to another chemical form can usually be considered in the design of sustained release systems for that drug. As long as the location rate and extent of metabolism are known and the rate constants for process are not too large, successful sustained release product can be developed.

There are two factors associated with the metabolism fo some drugs however which present problems for their use in sustained release systems. One is the ability of a drug it included or inhibits enzyme synthesis. This may result in fluctuation in drug blood level with chronic dosing. The other is fluctuation in drug blood level due to intestinal metabolism or through hepatic first pass effect.

SR systems for drugs, which are extensively metabolized, are possible as long as the rate of metabolism is not too great nor the metabolism variable with gastro-intestinal transit or other routes.

4.Elimination and biological half-life

The rate of elimination of a drug is quantitatively described by its biological half life (t ½). The half-life of a drug is related to its apparent volume of distribution V and its systemic clearance.

T ½ = 0.693 V/Cls = 0.693 V. AUC / Dose

Where,

Cls = Systemic Clearance

And is equal to the ratio of an IV administered dose to the total area under the curve versus time curve. It is difficult to define precise upper and lower limits for the value of the half-life of a drug that best suits it for sustained release formulations. In general however, a drug with a half- life of less than two hours should probably not be used.

Since such systems will require unacceptably large release rates and large doses. At the other extremes a drug with a half-life of greater than 8 hours should also probably not be used formulation of such a drug SR systems is unnecessary.

5.Duration of action

The biological half- life and hence the duration of action of a drug obviously plays a major role in considering a drug for SR systems drugs with short half – lives and high doses impose a constraint because of the dose size needed and those with long half-lives are inherently sustained.

6.Therapeutic Index

Drugs with a narrow therapeutic range require precise control over the blood levels of drug, placing a constraint on SR dosage forms.

The most widely used measured of the margin of safety of a drug is its therapeutic index (TI).

$$TI = TD_{50} / ED_{50}$$

Where,

TD_{50} = Median toxic dose

ED_{50} = Median effective dose.

1.4.3 Other factors in a controlled release formulation

1.Transit time

The transit time up to 2 hours approximately, limits the extent of prolongation possible with oral controlled release products.

2.Gastric emptying time

Variation in gastric emptying time and intestinal peristaltic activity affects the absorption. For example, aspirin microcapsules.

3.First pass hepatic effect

The drugs, which are suspected of undergoing a first pass hepatic metabolism, should not be formulated as an oral preparation. For example acetyl Salicylic acid, cortisone, morphine, indomethacin etc.

4.Environmental conditions

These vary for drugs along the gastro intestinal tract and certain drugs are preferentially absorbed at particular regions; vitamin B2 is absorbed high up in the gastro intestinal tract particularly in the upper duodenal area by an active transport mechanism that is saturable so that little is absorbed in the lower intestine.

5.Biological half – life

The biological half- life of the drug is very important. Drugs such as ampicillin, cloxacillin, furosemide, levodopa, and prophythiouracil have short half-lives and therefore require frequent dosing to maintain an adequate therapeutic level. Also, there is little medical rational for the use of a controlled release formulation in the case of drugs with a long biological half-life, since the drugs are inherently long acting.

1.5 Potential benefits derived from sustained release systems[13,14,27]

The potential benefits that a sustained release system may bring to use can be appreciated by a consideration of prolonged and efficient delivery of therapeutically effective dosages, patient compliance and localization of the therapy.

The bioavailability of drug molecules to the ailing tissue cells is governed by a sequence of pharmacokinetics processes release, absorption, absorption, distribution, metabolism and elimination. In some cases, these processes result in the inefficient bioavailability of the drug to the target tissue cells. The

bioavailability to a target tissue can be maximized and applying the principles of sustained release system can minimize the adverse side effects in non-target tissue.

Administration of drugs in convetntional dosage forms (except via i.v infusion at a constant rate) result in fluctuations of drug concentration in systemic circulation.

A well designed, sustained release system can reduce the frequency of drug dosing and also maintain concentration in blood circulation and target tissue cells. The pronounced fluctuations resulting from the conventional drug administration are likely to yield periods of no therapeutic effect when the drug concentration falls below minimum effective dose level (MED) and period of adverse reactions when the drug concentration exceeds the dose level. Drug concentrations can be maintain within a narrow therapeutic range by the use of sustained release systems that will also minimize the incidence and severity of adverse side effects.

The controlled or sustained release dosage forms are designed to complement the pharmaceutical activity of thye medicament in order to achieve better selectivity and longer duration of action.

1.5.1 Advantages of Sustained Release formulation [6,7]

1. **Improved Therapy**
    a. The dosage forms provide uniform drug availability blood levels unlike peak and valley pattern obtained by intermittent administration.

b. The incidence and intensity of undesirable side effects caused by excessively high peak drug concentration resulting from the administration of conventional dosage forms is reduced.
c. The missing of the dose cannont occur due to by patients non-compliance.

2. Patient convenience

Frequency of administration is reduced and this disturbance to the patient is less particularly at nigh (testing time).

3. Economy

a. Sometimes sustained release formulations are less expensive that conventional dosage forms.
b. Economy may also be affected due to decreased cost of nursing time for administration of drugs.
c. A decrease in the total dose of the drug necessary.

4. In a sustained release formulation the active ingredient is released at a predetermined rate for a predetermined period.

5. A more efficient utilization of the drugs in the body; example-controlled release aspirin provides sufficient drug so that an awakening, the arthritic patients has symptomatic relief.

6. Patient acceptance of the product compared to conventional dosage form.

1.5.2 Disadvantages

1. Usually the amount of drug in a sustained release dosage form in 3-5 times and if a dosage form is used improperly e.g. by chewing instead of swallowing, the patient would receive an overdose. Hence only such

drug, which possesses a substantial margin of safety, can be presented in sustained release dosage form.

2. Improper formulation may result in excessive dosage or the drug release may not be complete.
3. In case of accidental failure of the product effective antidote may be difficult to employ.
4. Sustained release dosage forms are sometimes costlier because of the technology involved in producing the formulation.
5. Sustained release medications should not be used with persons known to have impaired or erratic gastrointestinal absorbing or kidney troubles.
6. The physician has less flexibility in adjusting dosage regimens. This fixed by dosage form design.
7. It is difficult to formulate an ideal sustained release dosage form i.e . zero order delivery system.
8. Not all drugs are suitable candidates for formulation as prolong action medication. Table lists specific drug characteristics the would preclude formulation in per oral sustained release forms.

1.6 Compounds that are unsuitable for controlled release[28,29]

1. Short elimination half- life.
2. Long elimination half-life
3. Narrow therapeutic index
4. Large doses.
5. Poor absorption
6. Active absorption
7. Low or slow solubility.

8. Time courses of circulating drug levels different to that of pharmacological effect.
9. Extensive first pass clearance.

Characteristics of drugs unsuitable or oral sustained release forms

Characteristics	Drugs
• Not effectively absorbed in the lower Intestine	Riboflavin, Ferrous salts
• Absorbed and excreted rapidly, short Biological half –life (<1hr)	Penicillin, furasemide
• Long biological half-life (>12hr)	Digoxin, Diazepam
• Large doses required (>1g)	Sulfonamide ‘
• Cumulative action and undesirable effects, drugs with low therapeutic Indices.	Phenobarbital, Digitoxin
• Precise dosage titrated to individualize required.	Anti coagulants Cardiac
• NO clear advantage for sustained release Formulation	Griseofulvin

1.7. Designing of controlled release formulations[13,21].

From past few yeas considerable important has been given to the development of new drug delivery systems known as controlled release dosage formulations. Such interest is base largely on the fact that controlled release drug

products have established and retained a place in the market based on their uniqueness and their clinical advantages in the practice of medicine.

Controlled release dosage forms are those dosage formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of drug to a tissue. Drug release from these systems should be at a desired rated, predictable and reproducible.

Controlled release dosage forms have been referred to as delayed action, extended action, gradual release prolonged release, repeat action, slow release, sustained release, depot, retard, timed release, targeted, intelligent, novel and therapeutic dosage forms.

They provide one or more of the following benefits or advantages

1. Controlled administration of a therapeutic dose at a desirable delivery rate.
2. Maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment.
3. Maximization of efficacy- dose relationship
4. Reduction of adverse side effects.
5. Minimization of the needs for frequent dose in take.
6. Enhancement of patient compliance.
7. More efficient drug utilization by the body.

Because of their relatives ease of production and cost, compared with other methods of sustained or controlled delivery dissolution and diffusion controlled

systems have classically been of primary importance in oral delivery of medication. Most of the SR or CR systems are solids, although a few liquids, suspensions have been recently introduces, the classification of such system can be as follows.

1. Dissolution controlled systems
2. Diffusion systems
3. Dissolution and diffusion controlled systems
4. Osmotically controlled systems
5. Ion exchange systems

1.7.1. Dissolution Controlled Systems[10,16,36]

Drug with a slow dissolution rate demonstrates sustaining properties, since the release of drug will be limited by the rate of dissolution. This includes preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material or incorporating it into a tablet with a slowly dissolving carrier.

The dissolution process at steady state is described by the Noyes-Whitney equation, $d_c / dt = K_d A(C_s-C) = D/h A (C_s-C)$

Where

d_c / dt = Dissolution rate

K_d = Dissolution rate constant

D = Diffusion coefficient

C_s = Saturation solubility of the solid

C = Concentration of solute in the bulk solution

1.7.2.Diffusional Systems[10,11]

Diffusion systems are characterized by the release rate of drug being dependent on its diffusion through an inert membrance barrier. Usually, this barrier is an insoluble polymer. In general two types of subclasses of diffusional systems recognized they are,

1. Reservoir devices
2. Matrix devices

Reservoir devices

Reservoir devices are characterized by a core of drug the reservoir surrounded by a polymeric membrane. The nature of the membrance determisnes the rate of release of drug from the system. A schematic description of this process as shown in

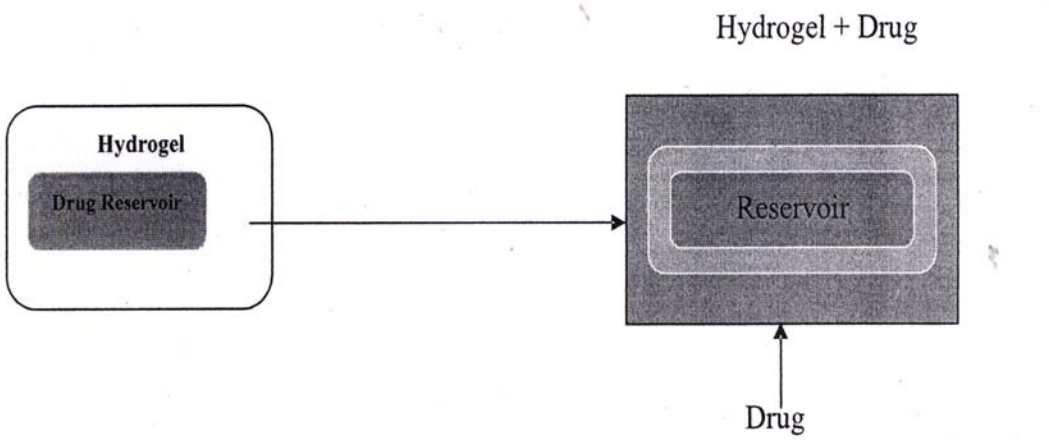


Fig. 2 Schematic depiction of drug release from a Hydrogel-based reservoir delivery system

The process of diffusion is generally described by Fick's equation.

$$J = -D\, d_c/dx$$

Where,

J = flux (amount / area time)

D = Diffusion coefficient of the drug in the membrane (area/time)

Advantages:

1. Zero –order delivery is possible.
2. Release rate variable with polymer type.

Disadvantages:

1. Potential toxicity if systems fails.
2. System must be physically removed from implant sites.
3. Difficult to delivery high molecular weight compound
4. Generally increased cost per dosage unit.

Matrix devices

It consists of drug dispersed homogeneously throghtout a polymer matrix as shown in

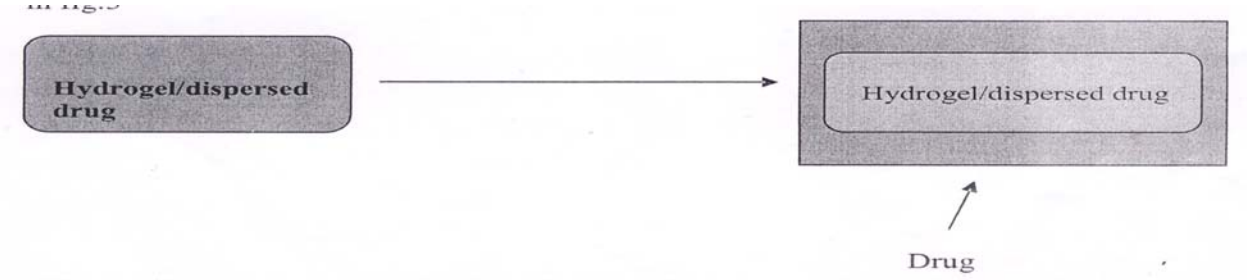


Fig.3. Schematic depiction of drug-release from a Hydrogel based matrix delivery system

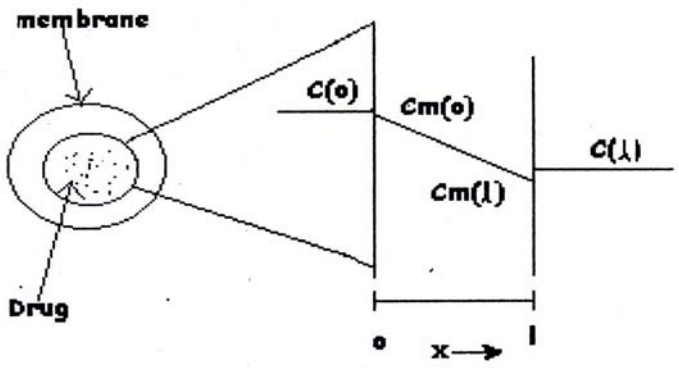


Fig.4. Schematic representation of a reservoir diffusion device. Cm (o) and Cm (1) represent concentrations of drug at the inside surfaces of the membrane and C (o) and C (1) represent concentration in the adjacent regions

In the model drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior.

The rate of drug availability is controlled by the rate of penetration of the dissolution medium throght the matrix and to the surface of the unit. As the drug dissolves, the diffusion path length increases because the polymer matrix is insoluble. With proper design of the system, an initial loading dose can be provided from the drug particles on or near the surface of the tablet.

Once pores have been created, drug release will slow down. Obviously rate of release will not be zero- order, as may be desired, because as the diffusion length

increases, the rate of dissolution falls, however, if one uses a slowly dissolving polymer matrix, where the matrix itself dissolved at a certain rate so as to keep the diffusional length more or less the same, it can result in a zero-order release.

The following equation describes the rate of release of drug dispersed in an inert matrix systems, have been derived by Higuchi,

$$dM/dh = C_0 dh - Cs/2$$

1.7.3. Dissolution and diffusional controlled release systems[10,11,21]

Strictly speaking, therapeutic systems will never be dependent on dissolution only or diffusion only. In practice, the dominant mechanim for release will over shadow other processes enough to allow classification as either dissolution rate – limited or diffusion controlled. A typical systems is shown in fig.

A simple expression describing release from all there of these erodible devices is,

$$M_t/M = [1\text{-}1\text{-}J_0 t/C_0 a]^n$$

Where,

- n = 3 for a sphere, n=2 for a cylinder and n=1for a slab.
- a = the radius of a sphere or cylinder or the half height of a slab.
- M_t = the mass of a drug release at time t.
- M = the mass released at infinite time.

Advantages:

1. Easier to produce than reservoir devices.
2. Can deliver high molecular weight compounds
3. Removal from implant sites is not necessary.

Disadvantages:

1. Difficult to control kinetics owing to multiple processes of release.

2. Potential toxicity of degraded polymer must be considered.

Potential advantage of sustained drug therapy

1. Avoid patient compliance problems.
2. Employ less total drug.
    a. Minimize or eliminate local side effects.
    b. Minimize or eliminates systemic side effects.
    c. Reduction in drug activity with chronic use or less potentiation.
3. Oral controlled release systems
4. Infusion pumps
5. Implantable devices (Mini pumps)

The two types of the controlling mechanisms ar used in the design of controlled release drug delivery systems.

1. Rate controlling by diffusion process

The release of drug molecules from the delivery is controlled by the molecular diffusion of drug molecules in and / or across the barrier medium within or surrounding the delivery systems. In polymer membrane permeations controlled drug delivery systems, a drug formulations is totally or partially encapsulated within is covered by a rate controlling polymeric membrane with a specific permeability. The drug reservoir can be it solid, suspension or solution form. The polymeric membrane can be fabricated from a homogeneous (or a heterogeneous) membrane. The encapsulation of drug formulation inside the reservoir compartment can be accomplished by injection molding, capsulation, micro encapsulation or other techniques.

2. Rate controlling by modulation process

In this type of rate– controlled drug delivery, the release of drug

molecules from the delivery system is slow and very limited by molecular diffusion process alone, and can be facilitated by the energy supplied externally or activated by some physical processes. The rate of drug release is the modulated by the energy or the physical processes applied such as osmotic pressure or hydrodynamic pressure or vapour pressure or modulated mechanically or magnetically.

Oral controlled release systems

The oral route is the most convenient and common mode for administration of controlled release systems.

The systems have gained importance because of the technological advance made in fabrication, which helps in achieving zero order release rates of therapeutic moiety. The majority of oral controlled release systems rely on dissolution, diffusion, or a combination of both mechanisms to generate slow release at drug to the gastro intestinal milieu. Starting with limited data on a drug candidate for sustained release such as does, rate constants for absorption and elimination, some elements of metabolism and some physicochemical properties of the drug, one can estimate a desired release rate for the dosage form, the quantity of the drug needed and a preliminary strategy for the dosage form to be utilized. The following are the major types of controlled release systems intended for oral use.

- Coated pellets.
- Mixed release granules.
- Erosion-core non-disintegrating tablets.
- Matrix tablets.
- Ion exchange and complexation methods.

- Micro encapsulation and microcapsule.
- Osmotically controlled oral preparations.

1.9 Type of prolonged action dosage forms[45]

there are many different types of prolonged action products. Balland and nelson discussed this subject exhaustively and listed many examples; Edward stempel discussed the various methods of prlonging the drug absorption and thus drug action. John G. Wagner listed out the mechanism and types of construction of oral prolonged action dosage form. W.A. Ritschel discussed various types of pre-oral and parenteral prolonged action dosage forms. The techniques used for oral and parenteral prolonged action preparations are listed below.

- Barrier coating
- Embedding the drug in slowly erodible matrix
- Skeleton type preparations.
- Repeat action preparations.
- Ion-exchange resin beads.
- Hydrophilic matrix / diffusion controlled matrix
- Polymer resin beads.

1.10. Components of controlled release devices[4,46]

A controlled release matrix system consists of the active agent and the polymer matrix or matrices that regulate its release. In selecting polymeric matrix, the following design criteria should be considered.

- Molucular weight and chemical functionality of the polymer must allow the proper diffusion and release of the specific active agent.

- Polymer functional groups should not react chemicals with the active agent.
- The polymer and its degradation products must be non-toxic to the environment.
- The polymer must be easily manufactured or fabricate into the desired product and should allow incorporation of large amounts of actives agents in the products without sacrificing its mechanical properties.
- The cost of the polymer should not be expensive which would cause a sustained release product to be non competitive.
- The various controlled release technologies cover a very broad spectrum of drug dosage forms. Controlled release technologies include, but are not limited to physical systems and chemical systems.
- Physical systems include, but are not limited, to reservoir with rate controlling membranes, such as microencapsulation, macroencapsultion and membrane systems; reservoir systems without rate-controlling membrane, such as hollow fiber, ultra microporous cellulose triacetate, and porous polymeric, or elastomeric matrices (e.g. nonerodible, polymerice, or elastomeric matrices, erodible, environmentral agent ingressions and degradable); laminated structures, including reservoir layers chemically similar or dissimilar to outer control layer, and other physical methods, such as sosmotic pump, or adsorption onto ion-exchange resins.
- Chemical systems include systems, but are not limited to chemical erosion of polymer matrices (e.g. heterogeneous, or homogenesous erosion), or biological erosion of a polymer matrix (eg heterogeneous , or homogeneous)
- Controlled release drug delivery systems may also be categorized under their basic technology areas, including but not limited to, rate-preprogrammed

drug delivery systems, activation-modulated drug delivery and site-targeting drug delivery system.

- In rate- preprogrammed drug delivery systems, release of drug molecules from the delivery systems, “preprogrammed” at specific rate profiles. This may be accomplished by system design, which controls the molecular diffusion of drug molecules in and /or across the barrier medium within or surrounding the delivery systems. Fick’s law of diffusion are often followed.
- In a site –targeting controlled release drug delivery system, the drug system targets the active molecule to a specific site or target tissue or cell.
- While a preferable mode of controlled release drug delivery will be oral, other modes of delivery of controlled release compositions according to this invention may be used.
- These include mucosal delivery, nasal delivery, ocular delivery, transdermal delivery, parenteral controlled release delivery, vaginal delivery, and intrauterine delivery.
- Another type of useful oral controlled release structure is a solid dispersion. A solid dispersion may be defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by eh melting (fusion), solvent, or melting –solvent method.

1.11. Matrix System[10,35,42]

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, retardant material and additives to form a tablet in which drug is embedded in a matrix of the retardant. Alternatively drug blends may be granulated prior to compression. The following table identified example of the three classes or retardant material

used to formulate matrix tablets, each class demonstrating a different approach to the matrix concept.

The first class consists or retardant that forms insoluble or “skeleton” matrices, the second class represents water-soluble materials that are potential erodible and the third class consists of polymers that form hydrophilic matrices.

Table -1

Materials used as retardants in matrix tablets formulations

Matrix Characteristics	**Material**
1.Insoluble, Inert	Polyethylene, Polyvinyl chloride, Methyl acrylate, Methacrylate co-polymer, Ethyl cellulose
2. Insoluble, Erodible	Carnauba wax, Stearyl alcohol, stearic acid, PEG.
3. Hydrophilic	Methyl cellulose, (400cps, 4000cps), Hydroxy ethyl Cellulose, HPMC (60HG, 90HG, 25cps, 40 00cps, 1500cps), Sodium CMC, Soduum alginate, carboxyl-Polyethylene.

Insoluble inert polymers such as polyethylene, polyvinylchloride and acrylate co-polymers have been used as the basic material for may marketed

formualations. Tablets prepared from these materials are designed to be suggested instant the not break part in the GI tract. Tablets may be directly compressed from mixture of drugs and ground polymer. However if ethyl cellulose is uded as the matrix former, a (wet) granulation procedure using ethanol can be employed. The rate limiting step in controlling release from these formulations is liquid penetration into the matrix unless channeling (wetting) agents are included to promote the permeation of the polymer matrix by water, allows drug dissolution and diffusion from the channel created in the matrix.

Formulations should be designed so that pore diffusion becomes rate controlling release is defined by equation 1,2. Drug bioavailability which is critically dependent on the drug. Polymer ratio, may be modified by inclusion of diluents such as lactose in place of polymer in low-milligram potency formlaitons.

Higuchi has provided the theroretic basis for defining drug release from inert matrices. The equation describing drug release form the planner surface of an insoluble matrix is.

$$Q = [[D\ C_g / T]\ [2A - C_s]\ t]\ ½ \text{ ----------(1)}$$

Q is the amount of drug released per unit, surface after time t.

E is porosity of the matrix.

D is the diffusion co-efficient of the drug in the elution medium

T is the tortuosity of the matrix

C_s is the solubility of the drug in the elution medium

A is initial loading dose of drug in the matrix.

Drug release in triggered by penetriaon of eluting media into the matrix dissolving the drug, there by creating channels through which diffusion take place.

A high tortuosity means that the effective averages diffusion path is large. The porosity term takes into account the space available for drug dissolution, an increased porosity results in increase drug release. Both porosity and tortuosity are functions of the amount of dispersed drug, the physico-chemical properties of the matrix, and dispersion charactestics of the drug in the matrix

If the drug is freely soluble in the elution medium that is Cs >> A, such that the dissolution rate is rapid, then equation (2), which describes the release or drug from a solution entrapped in an insoluble matrix applied.

$Q = 2A (D_t / TIT) ½$ ----------(2)

Release rate is directly proportional to the amount of dispersed drug A; it is proportional to A ½ for insoluble drug if 2A = Cs These expressions predict the plots of Q Vs t ½ be liner.

Release of water soluble drugs, however should be unaffected by the amount of liquid pH value, enzyme content and other physical properties of digestive fluids, unless the drug is in a salt form that precipitates within the matrix pores on dissolution when penetrated by acidic or basic media.

1.12. Biopharmaceutical Considerations[3,36,48]

The BCS is a scientific framework for classifying drug substances base on their aqueous and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account there major factor that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution solubility, and intestinal permeability. According to the BCS, drug substances are classified as follow

Class 1	:	High Solubility	-	High Permeability
Class 2	:	Low Solubility	-	High Permeability
Class 3	:	High Solubility	-	Low Permeability
Class 4	:	Low Solubility	-	Low Permeability

A.Solubility

The solubility class boundary is base on the highest dose strength of an IR product that is the subject of a bioaiver request, a drug substance is considered highly soluble when the highest does is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. the voluve estimate of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting volunteers with a glass (about 8 ounces) of water.

B.Permeability

The permeability class boundary is based indirectly on the extent of adsorption (fraction of dose absorbed, not systematic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent to be 90% or more of an administered dose base on a mass balance determination or a comparison to an intravenous reference dose.

C.Dissolution

In this guidance, an IR drug product is considered rapidly dissolving when no less than 85% of labeled amount of the drug substance dissolved within 30 minutes, using U.S. Pharmacoperia (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 500 ml or less in each of the following mediaa: (1) 0.1N HCL or Simulated Gastric Fluid USP without enyzmers (2) a pH 4.5 buffer, (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

The success of a therapy depends on selection of the t appropriated delivery systems as much as it depend on selection on the drug itself . A dosage form, whether conventional of CR, can have a significant effect on bioabailability and makes a difference between success and failure therapy.

For ocnvetional oral dosage forms, a major concern is bioavailability of a drug. Selection of dosage forms is base on how rapidly and completely drug is available. Both from institution as well as experimental obesrvaiton, systemic availability of a drug is maximum from an aqueous solution and minimum from a coated tablet, with suspension, capsule and tablet, showing intemediated bioavailabilities in that order. Deviation from this rule are some times observed. The picture however is different of CR formulations, where one rarely has a choice of solution or suspension dosage for not only bioavailability but also uniformity of drug input into the body .

12. Biopharmaceutical considerations

The rate and extent of drug absorption from CR dosage forms is determined by the rate of release from the dosage form. This is based on the assumption that absorption form the entire GI tract is efficient enough not be rate limiting. Although a common observation is less than from a conventional dosage form. Possible explanations for these observations are as follows.

- Drug release is not complete from a CR formulations specially for those designed release drug for period longer that 6 hr at a low release rate.

- There is a greater degree of reabsorpiton degradation and metabolism in the GI tract particularly for storable process or colonic delivery systems.
- First –pass metabolism for CR formulations may be higher.
- Drug release may be at a site of poor absorption, eg. The colon.
- Fewer dissolution media are available for CR dosage forms, especially in the terminal ileum.
- There is differential absorption from the GI tract i.e. drug absorption takes place in a limited area.
- GI residence of the dosage form may be variable and unpredictable.

As with conventional dosage forms, considerable differences in performances among different CR products of the same drugs are frequently observed. This will result in considerable variations in plasma drug profiles for similar doses.

Drug devices that are designed to stay in a particular segment of the GI tract eg. Bioadhesive systems have delayed gastric emptying and one must take into account the stability of the drug in that environment. Degradation due to pH or enzymes may reduce bioavailability of such dosage forms. Also single-units intended to stay at the pylorus or ileo-cecal junction may release enough drugs in their immediate vicinity to cause local toxicity or irrition. Design must also account for possible bacterial degradation and variable and poor absorption from the colon and rectum.

1.13.Pharmacokinetics consideration in the design of sustained release drug delivery systems.

The objective in designing sustained release systems to deliver drug at a rate necessary to achieve and maintain constant drug blood level. Attainment of an

absorption rate equivalent of the drug in the body is the principle underlying the design of prolonged action dosage forms. To design and fabricate an effective sustained release dosage forms.The fraction of the total dose into the gastrointestinal tract called “loading dose “ is consistent with the drugs intrinsic availability of absorption. The remaining fraction of the total dose is then release as rapidly as required for some desirable period of time. Thus the rate of drug absorption from the maintenance dose into the body should be equivalent to rate of drug eliminated the body by all processes, the time for which desired intensity of pharmacological response is required.

2. REASONS FOR STUDY

Ondansetron Hydro chloride is short acting drug for management of nausea and vomiting. It is absorbed from GIT and peak plasma concentration have occured 1 to 2 hours after dosing. It undergoes extensive first pass metabolism in the liver and is excreted mainly in the urine as inactive metabolites.

For sustained or controlled release it will helps in reduction of its side effects due to high concentration at the absorption site.

3. LITERATURE SURVEY

Barry, et al (Us Patent no: 5,055,306; 1991) prepared sustained release formulations of 5HT3 antagonist substance presented in the form of a tablet, said tablet comprising sufficient granules to provide a predetermined dose or number of

doses of the pharmacologically active substance and effervescent or water-dispersible ingredients, each of said granules having a diameter of preferably between 0.5 and 2.5 mm and comprising: a) a core comprising one or more phrmacologically active substances and preferably one or more excipients; and b) and coating covering substantially the whole surface of the core and comprising 100 parts of a water insoluble but water swellable acrylic polymer 20 to 70 parts of a water soluble and hydroxyl and cellulose derivative, the weight of the coating being form 2 to 25 % of the weight of the core. A method for preparing this effervescent of water- dispersible tablet formulations is also core. A method for preparing this effervescent of water- dispersible tablet formulation is also provided. Such formulations enable large dosages in sustained – release form to be more easily administered to patients.

Zhang Y, Huang G, Han J, Yu P (2006); prepared the ondansetron hydrochloride sustained – release tablets and studied the influencing factors, on the ondansetron hydrochloride sustained –release tablets, using the hydroxypropylmethylcellulose (HPMC) as the matrix material. They investigated methods, the alcohol content in adhesives, and the pH of the dissolving solution on the release of ondansetron hydrochloride from sustained release tablets. One the basis of pharmaceutical formulation studies, the best formulation and preparation methods were screened out according , ondansetron hydrochloride sustained – release tablets had good drug release behavior for in 12 h in vitro studies. To prepare the formulation from drug and polymer ratio for 1:2 ,1:3. and evaluation by the dissolution at phosphate buffer PH

6.8 in good drug release .

Landau et al (US patent no: 7,094, 786; 2006). Developed the method for the treatment of nausea and vomiting in a patient suffering from nausea and vomiting by administering 4-(2-fluorophenyl)-6 methyl12-(1-piperazinyl) thieno [2,3-D] pyrimidine. i..e. the use of 5-HT. sub .3 receptor antagonists such as ondansetron, granisetron and tropisetron has been shown to be less effective for delayed nausea and vomiting than for acute symptoms. In addition, efficacy of the 5-HT. sub. 3 receptor antagonists appears to be less pronounced for moderate emetogenic chemotherapy regimens than for cisplatin-containing regimens. Further, control over nausea appears to be significantly less than control over vomiting, further, the efficacy of the agents appears to diminish across repeated days and across repeated chemotherapy cycles.

Srinivas Reddy et al. (2003) The objective of the present study was to develop once-daily sustained-release matrix tablets of nicorandil, a novel potassium channel opener used in cardiovascular diseases. The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC), Eudragit RL Trang Web nay coi cung hay, vao coi the -100, Eudragit RS-100, and polyvinylpyrrolidone were used as granulating agents along with hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, and sodium alginate. The results of dissolution studies indicated that formualtion F-I (drug –to-HPMC, 1:4; ethanol as granulating agent) could extend the drug release up to 24 hours. In the further formulation development process, F-IX (drug-to-HPMC, EC 4% wt/vol as granulating agent), the most successful formulation of the study, exhibited satisfactory drug release in the initial hours, and the total release pattern was very close to the theoretical release profile. All the formulations (except F-IX) exhibited diffusions-dominated

drug release. The mechanism of drug release from F-IX was diffusion coupled with erosion.

4. AIM & OBJECTIVE

The main objective of this work is to investigate the possibility of sustained release dosage forms for the drug in ondansetron hydrochloride by usings different grades of HPMC polymers by diffusin controlled matrix.

For this investigation in various formulation (formulation I-formulation –V)at different polymers for HPMC K4 M, HPMC K15 M, HPMC K100LVP were made by using drug 4 mg.

The aim of this study to formulate and evaluate the release pattern of drug from sustained release matrix tablets.

5. PLAN OF WORK

1.Preformulation study

2.Dose calculation

3. Preparation of sustained release tablets using the polymer at various concentrations.

4.Evaluation of Physical parameters

a. Weight variation
b. Hardness
c. Thickness
d. Friability

5.Invitro evaluation of tablets

6.Assay

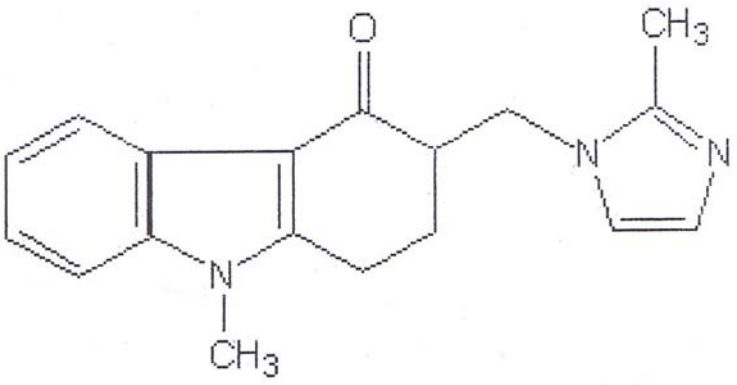
7.Accelerated stability studies of tablet.

6. Drug and Excipeints Profile

6.1 Drug Profile[19,20,33,35,38]

The active ingredient ondansetron hydrochloride tablets is ondansetron hydrochloride(HC1) as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5 -HT3 receptor type.

Structural Formula:



.HCI.2H_2O

Chemical Name: (±) 1, 2, 3, 9-tetrahydro-9-methyll3 [(2methyl – 1 H-imidazol- 1-yl)methyl]-4H-carbazol -4-one,monohy droch1oride, dihydrate.

Molecular Formula: C $_{18}$H $_{19}$N$_{30}$ .HC12H20.

Molecular Weight: 365.9

Colour: white to off-white powder.

Solubility: Sparingly soluble in water and in alcohol: Soluble in Methanol, slightly soluble in Methylene chloride.

Clinical Pharmacology

Pharmacodyamics

Ondansetron is a selective 5-HT3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine - receptor antagonist. Serotonin receptors of the 5 -HT3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of sero tonin from the enterochromaffin cells of the small intestine. In humans, urinary 5 -HIAA (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT3 receptors and initiate the vomiting reflex.

In normal volunteers, single intravenous doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

Ondansetron does not alter the respiratory depressant effects produced by alfe ntanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been studied.

Pharmacokinetics

Ondansetron is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8 mg tablet, is appi oximately 56%

Ondansetron systemic exposure does not increase proportionately to dose. AUC from a 16 mg tablet was 24% greater than predicted from an 8 mg tablet dose. This may reflect some reduction of first-pass metabolism at highei oral doses Bioavailability is also slightly enhanced by the presence of food but unaffected by antacids.

Ondansetron is extensively metabolized in humans, with approximat ely 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation. Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination.

Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, C max, and T1/2 of ondansetron was observed 1. This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended in humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

Gender differences were shown in the disposition of ondansetron given as a single dose. The extent and rate of ondansetron's absorption is greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron levels. These higher plasma levels may in part be explained by differences in body weight between men and women. It is not known whether these gender –related differences were clinically important.

Indications and Usage for Ondansetron

Prevention of nausea and vomiting associated with highly emeto genic cancer chemotherapy, including cisplatin 50 mg/rn ^{2}

Prevention of nausea and vomiting associated with initial and repeat courses of moderately em the cancer chemotherapy.

Prevention of nausea and vomiting associated with radiotherapy in patient s receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.

Prevention of postoperative nausea and/or vomiting. As with other antiemetics. routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ondansetron hydrochloride tablets are recommended even where the incidence of postoperative nausea and/or vomiting is low.

Contraindications

Ondansetron hydrochloride tablets are contraindicated for patients known to have hypersensitivity to the drug.

Warnings

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5 -HT3 receptor antagonists.

Precautions

General

Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of ondansetron in

patients following abdorni nal surgery or in patients with chemotherapy-induced nausea, and vomiting may mask a progressive ileus and/or gastric distension.

Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.

Drug Interactions

Ondansetron does not itself appear to induce or inhibit the cytochrome P - 450 drug- metabolizing enzyme system of the liver. Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP 1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. On the basis of available data, no dosage adjustment is recommended for patients on these drugs.

Phenytoin, Carbamazepine, and Rifampicin

In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs[3,4]

Tramadol

Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron

may be associated wit h an increase in patient controlled administration of tramadol[8,9]

Chemotherapy

Tumor response to chemotherapy in the P-388 mouse leukemia model is not affected byondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover study in 76 pediatric patients, I.V. ondansetron did not increase blood levels of high-dose methotrexate.

Use in Surgical Patients

The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic effects were not seen in 2 -year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg/day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of

ondansetron up to 15 mg/kg/day did not affect fertility or general reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects

Pregnancy Category B. Reproduction studies have been perform ed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Geriatric Use

Of the total number of subjects enrolled in cancer chemotherapy -induced and postop erative nausea and vomiting in US - and foreign-controlled clinical trials, for which there were subgroup analyses, 938 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subject s, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.).

Adverse Reactions

1. Difficulty in breathing, wheezing, shortness of breath

2. Fast or irregular heart beat.

3. Constipation or diarrhoea.

4. Headache

5. Dry mouth

6. Stomach pain

7. Skin rash, itching, swelling of the face, tongue , throat, hands and feet.
8. Fever and chills.

Drug Abuse and Dependence

Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addition studies.

Overdosage

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual intravenous doses as large as 150 mg and total daily intravenous doses as large as 252 mg have been

inadvertently administered without significant adverse events. These doses are more than 10 times the recommended daily dose.

In addition to the adverse events listed above, the following events have been described in the setting of ondansetron overdose: “Sudden blindness” (amaurosis) of 2 to 3 minutes’ duration plus severe constipation occurred in 1 patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg of ondansetron hydrochloride tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second -degree heart block was observed. In all instances, the events resolved completely.

Ondansetron Dosage and Administration

1) Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer
Chemotherapy

The recommended adult oral dosage of ondansetron hydrochioride tablet is 24 mg given as three 8 mg tablets administered 30 minutes before the start of single -day highly emetogenic chemotherapy, including cisplatin 50 mg/m^2. Multiday, single-dose administration of a 24 mg dosage has not been studied.

Pediatric Use

There is no experience with the use of a 24 mg dosage in pediatric patients.

Geriatric Use

The dosage recommendation is the same as for the general population.

2) Prevention of Nausea and Vomiting Associated With Moderately Emetogenic Cancer Chemotherapy

The recommended adult oral dosage is one 8 mg ondansetron hydrochloride tablet given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose.one 8 mg ondansetron hydrochloride tablet should be administered twice a day (every 12 hours) for1 to 2 days after completion of chemotherapy.

Pediatric Use

For pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric patients 4 through 11 years of age, the dosage is one 4 mg ondansetron hydrochloride tablet given 3 times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4 mg ondansetron hydrochloride tablet should be administered 3 times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

Geriatric Use

The dosage is the same as for the general population.

6.2 Additives used in formulation of Ondansetron Hydrochloride sustained release tablets[34,41,43,45].

1. HYDROXYPROPYL METHYL CELLULOSE

1. **Nonproprietary Name**

BP : Hypromellulose

JP : Hydroxyprophyl methyl cellulose

PhEur: Methylhydroxy prophyl cellulosum

USP : Hydroxypropyl methyl cellulose

Synonyms

Benecel MHPC; Cellulose, Hyroxypropyl methyl ether; E464; HPMC; Methocel; Methycellulose propylene glycolether; methyl Hydroxypropyl cellulose, Metolose; Pharmacoat,

Chemical Name and CAS Registry Number

Cellulose, 2- Hydroxypropyl methyl ether.

Empirical Formula	**Molecular weight**
O-methylated and O-(2-hydroxypropylated cellulose)	10,000-15,00,000

Functional Category

Coating agent; film former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity – increasing agent.

Applications is Pharmaceutical Formulation or Technology

Hydroxyl propyl methylcellulose is widely used in oral and topical pharmaceutical formulation.

In oral products, hydroxypropyl methylcellulose in primary used as a tablet binder, in film coating, and as an extended-release tablet matrix. Concentrations of between 2-5% w/w may be used as a binder in either wet or drug granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels 10-80% w/w in tablet and capsule, depending upon the viscosity grades concentrations between2-20% w/w are used as film-forming solutions to film coat tablets. Lower viscosity grades are used in aqueous film-coating solutions while higher viscosity grades are used with organic solvents.

Hydroxypropyl methylcellulose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hydroxypropyl methycellulose produces solutions of greater clarity, with fewer undispersed fibres present, and is therefore preferred in

formulations for ophthalmic use. Concentrations of between- 0.45-1.0% w/w made be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hydroxypropyl methylcellulose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formulation of sediments.

In addition, hydroxypropyl methylcellulose is used in the manufacture of capsules, as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Applications Table-2

Sr. No	Use	Conc% w/w
1)	Binder	2-5%
2)	Film-former	2-20 %
3)	Thickening agent	0.45-1.0 %

Viscosity

Table-3

Sr. no	**Grades**	**Nominal (µm)**	**Viscosity (m Pas)**
1	K 100LVP	100	80-120
2	K 4 M	4000	3000-5600
3	K 15 M	15000	12000-21000

Description

Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

Typical Properties

Acidity /alkalinity: PH=5.5-8.0 for a 1% w/w aqueous solution

Density (bulk): 0.341 g/cm^3

Density (tapped) : 0.557 g/cm^3

Density (true) : 1.326g/cm^3

Melting point; Browns at 190º-200^{0}C; chars at 225ºC-230^{0}C. Glass transition temperature is 170ºC-180^{0}C.

Solubility

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethame, mixtures of methanol and dichloromethane, and mixtures of water and alcohol, certain grades of hydroxpropyl methylcellulose are soluble in aqueous acetone solutions, mixtures of dichloromethane and proan -2-01, and other organic solvents.

Stability and storage conditions

Hydroxypropyl methylcellulose powder is a stable material although it is hygroscopic after drying.

Incompatibilities

Hydroxypropyl methylcellulose is incompatible with some oxidizing agents. Since it is nonionic, hydroxypropyl methylcellulose will not complex with metallic salts or ionic organics to form insoluble precipitates.

2. MICROCRYSTALLINE CELLULOSE (AVICEL PH 101)

Synonyms : Avicel PH; Emcocel; Pharmacel.

Formula : $(C_6H_{10}O_5)_n$ -36000

Where n = 220

Funtional Category : Tablet and Capsule diluent, Disintegerant.

Description : White, odourless, tasteless, crystalline powder composed of porous particle. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Typical Properties : LOD -6.0% to 7.0%

Bulk Density = 0.32 g/cm^3

Tapped Density = 0.45 g/cm^3

Melting Point = 260ºC-27^{0}C

Moisture Content = Less than 5 % w/w

Particle size distribution: Mean particle size is 20-200 µm **Solubility :** slightly soluble in 5 % w/v NaOH solution ; practically insoluble in water, dilute and most organic solvents.

Table-4

Grade	Nominal particle size (µm)	Particle size analysis		Moisture Content (%)
		Mesh size	Amount retained %	
Avicel PH 101	50	60 200	1.0 30.0	5.0

Applications:

Table-5

Sr.No	Use	Conc.%
1)	Adsorbent	20-90
2)	Anti-adherent	5-20
3)	Capsule binder/diluents	20-90
4)	Tablet disintegerant	5-15
5)	Tablet binder/diluents	20-90

3. STARCH – 1500

Nonproprietary Names

PhEur: Strach, pregelatinized

USP; Pregelatinized Starch

Synonyms

Compressible starch. Instastarch, Lycatab PGS, Pharma-Gel, Prejel, Sepistab ST 200, Starch 1500.

Chemical Name of CAS Registry Number

Pregelatinized starch (9005-25-8)

Empirical Category

$(C_6H_{10}O_5)_n$

Where n = 300-1000

Functional Category

Tablet and capsule diluent, tablet and capsule disintegrant ,tablet binder.

Applications in Pharmaceutical formulation or Technology

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent, and disintegrant.

In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pegelatinized material may be used as a tablet binder in dry compression processes. In such processes pregelatinized starch is self lubricating. Pregelatinized starch may also be used in wet granulation processes.

Table-6

Use	Concentration (%)

Diluent	5-75
Tablet binder (direct compression)	5-20
Tablet binder (wet granulation)	5-10
Tablet disintegent	5-10

Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder, it is odorless and has a slight characteristic taste.

Typical Properties

Acidity /alkalinity ; PH=4.5-7.0 for a 10% w/v aqueous solution.

Density (bulk): 0.586g/cm^3

Density (tapped); 0.879g/cm^3

Density (true): 1.516g/cm^3

Angle of repose : 40.7^0

Flowbility : 18-23%

Solubility

Practically insoluble in organic solvents, slightly soluble to soluble in cold water, depending upon the degree of pregelatinization.

Stability and storage conditions

Pregelatinized starch is a stable, through hygroscopic material, which should be stored in a well-closed container in a cool, dry, place.

4. LACTOSE MONOHYDRATE

Synonyms: Pharmatose, SorboLac, Super-Tab, Tablettose, Lactopress, Microfine.

Formula : $C_{12}H_{22}0_{11}$ (340.30) Anhydrous

$C_{12}H_{22}0_{11},.H20$ (360.31) Monohydrate

Funtional Category : Tablet & capsule Diluent.

Description: lactose occurs as white to off-white crystalline particles or powder, odourless, slightly sweet tasting, a lactose in approximately 15% as sweet as sucrose, while a lactose is sweeter than the a lactose.

Typical Properties : LOD = 0.5%-1.0%

Water	=	4.5%-5.5%
Bulk Density	=	0.62 gm/cm^3
Tapped Density	=	0.94/cm^3
True Density	=	1.552
Melting point	=	201ºC-202ºC

Moisture Content=Approx. 5% w/w of water of crystallization & normally ranges between 4.5%-5-5%.

Solubility

Table-7

Sr.No	**Solvents**	**Solubility at 20°C or Unless otherwise stated**
1	Chloroform	Practically Insoluble
2	Ethanol	Practically Insoluble
3	Ether	Practically Insoluble
4	Water	1 in 4.63 1 in 3.14 at 40°C 1 in 2.04 at 50°C 1 in 1.68 at 60°C 1 in 1.07 at 80°C

Applications : It is widely used as filler or diluents in tablets, capsules & also in dry powder inhalations.

Various lactose grades are commercially available that have different particle size distribution and flow characteristics. Fine grades of lactose are used in preparation of tablets by wet granulations method, since of fine size permits better mixing with other formulation ingredients and utilized binder more efficiently

Spray dried lactose is directly compressible grade lactose which is more fluid and more compressible than crystalline form. Spray dried lactose is composed of pure a lactose monohydrate and small amount of amorphous lactose.

5. AEROSIL

Non proprietary name:

Colloidal silicon dioxide

Functional category:

Pharmaceutical aid (suspending agent, tablet and capsule adjuvant)

Synonyms:

Colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed, aerosol, cab-o-sil, syloid.

Molecular weight:

60.08

Characteristics:

Submicroscopic, light, loose, bluiswhite, odourless, tasteless, non-gritty amorphous powder.

Solubility :

Insoluble in purified water, forms a colloidal dispersion, soluble in hot solutions of alkali hydroxide, insoluble in acids, except hydrofluoric, insoluble in organic solvents.

Stability and storage conditions:

Colloidal silicon dioxide is hygroscopic but absorbs large quantities of water without liquefying. Store in well closed container.

Uses:

- Drying agent for hygroscopic materials, absorbent dispensing agent for liquids in powders or suppositories.
- Glidants and antiadherents in tableting processes and encapsulation.
- Thickening and suspending agent in gels.

6. Magnesium Stearate

Synonyms Stearic acid magnesium salt,
Magnesium octadecanoate

Chemical Name Octadecanoic acid magnesium

Nonproprientary Names

BP- Magnesium stearate
PhEur – Magneshi stearate
USPNF – Magnesium stearate

Description

Magnesium stearate is a fine, white, precipitated, milled impalatable powder of low bulk density, having a faint, characteristic odor and taste. The powder is greasy to touch and readily adheres to skin.

Applications

Magnesium stearate is widely used in cosmetics, foods, and pharmaceuticals. It is primarily used as lubricant in capsule and tablet manufacture at concentration between 0.25-50% concentrations.

7. Material and Method

PREFORMULATIONS STUDIES

INDENTICATION AND CHARACTERIZATION OF ONDANSETRON HYDROCHLORIDE

Infra-Red Absorption spectrum

The IR spectrum of Ondansetron Hydrochloride was determined and recorded using IR Spectro photometer. The KBr pellet method was used for preparation of ondansetron Hydro chloride.

UV Spectrophotometer method

Weighed accurately 100 mg pure ondansetron drug was taken and dissolved in 100ml of water. This made up to 100 mg/ ml solution. From this stock solution from 0.5ml was taken and diluted with distilled water.The absorbance was measured at 310 nm using UV- spectrophotometer.

Melting point

The melting point of ondanseton was determined by capillary method.

Dose Calculation

initial Dose (Di) = 2mg

Biological half life of the drug (t1/2) = 3.1 hours

Elimination rate constat = 0.693/3.1 = 0.2235 hr-1

Time to reach peak plasma conc. (Tp) = 1.5 hrs

time over which sustained dose is released (T_d) = 12 hrs

Desired constant release from sustained dose = K_0 = D1Xkel

= (2) x (0.2235) = 0.447 $mghr^{-1}$

= D1 = $K_{o/}K_{e1}$ = D_s/K_{e1}x T= (since $K_o=D_s/T$)

where Ds = sustained dosage

T= Time over which sustained dose is release.

$D_s = D_1$ X $K_{el}1$ x T

2 x 0.2235 x 12- 4.364

Corrected initial dose = (Di)

2-(1.5 x 2x 0.2235)

= 2-0.6705

= 1.3295

Corrected initial dose D_i = 1.3295

Total Dose = Di + D_s = 1.3295+ 4.364 = 5.69

5.69 mg= 5mg.

7.1 LIST OF INSTRUMENTS

Table-8

Instruments used in the formulation and analysis of Ondansetron Sustained Release Tablets.

Sr.NO	NAME OF INSTRUMENTS	MANUFACTURER	APPLICATION
1	Tap Density Tester	Electrolab	Determine Bulk Density of Granules
2	Distal weighing balance	Sartorius	Used for weighing
3	Rotary machine	Rimeck	Used for compression of granulation
4	Hardness tester	Pfizer	Used for checking Hardness
5	Vernier Caliper	Mirotoyo corps	For checking Thickness
6	Tray Drier	Mixfill	For Drying Granulation
7	Conventional Coating Machine	KSD	For Tablet Coating
8	UV spectrophotometer	Mapada /Techcomp	Assay of Drug

The following materials were obtained from following commercial sources.

Table-9

1) Ondansetron Hydrochlorided, Dihydrate - Nactco Pharma Ltd, Hyderabad

2) Lactose Monohydrate - DMV International

3) Microcrystalline Cellulose (pH 101) - Signet chemicals

4) Pregelatinized starch - Colorcon Asia Pvt. Ltd

5) HPMC (K4M,K15M, K 100M) - Coloron Asia Pvt. Ltd

6) Magnesium Stearate - Parag Fine Organics

7) PEG 6000 - VaSudha Chemicals Pvt. Ltd

8) Talc -Nice chemical Pvt limited

9) Dibutyl Phathalate - Merck Specialities Pvt. Ltd

10) Titanium Dioxide - Kronos Internaitonal

11) Isopropy1 Alcohol - Lee Chang Yung chemical Pvt.Ltd

The following materials were obtained from commercial sources and Used as received.

Ingredients used in the formulation development of Ondansetron Sustained Release Tablets-

Table-10

Sr.No	NAME OF INGREDIENTS	SPECIFICATION	NATURE	APPLICATION
1.	Ondansetron Hydrochloride Equivalent Ondansetron	USP	Solid	Active Drug
2	Lactose Monohydrate	IP	Solid	Diluent
3	Microcrystalline celluslose	IP	Solid	Diluent
4	Starch	BP	Solid	Binder
5	Purified Water	IH	Liquid	Vehicle
6	Microcrystalline Cellulose	IP	Solid	Lubricant
7	Magnesium stearate	IP	Solid	Lubricant

Ingredients used in the Film Coating

Table-11

Sr.No	NAME OF	SPECIFICATION	NATURE	APPLICATION

	INGREDIENTS			
1.	Hydroxypropylmethycellulose	IP	Solid	Polymer
2	Dibutyl Phthalate	IP	Liquid	Plasticizer
3	Polyethylene Glycol 6000	IP	Solid	Plasticizer
4	Talc	IP	Solid	Glidant
5	Titanium Dioxide	IP	Solid	Opacifier
6	Isopropyl Alcohol	IP	Liquid	Vehicle
7	Dicholoromethane (Methylene Chloride)	BP	Liquid	Vehicle

Standard Curve for ondansetron hydrochloride

Procedure

100 mg of ondansetron hydrochloride was accurately weighed and then dissolved in 100 ml of water. This solution is having concentration 100 mg/ml. From this stock solution 5,10,15,20, 30,40,50 µg/ml by distilled water. Absorbance was measured at 310 nm using UV-spectrophotometer (MAPADA) .The standard plot is plotted for absorbance verus concentration .

Table No 12 . Standard Curve for ondansetron hydrochloride

Sr.No	Concentration in µg/ml	Absorbance at 310 nm
1	5	0.2096
2	10	0.4352
3	15	0.6148
4	20	0.8412
5	30	1.2110
6	40	1.6431
7	50	2.0150

R - 0.9997

A - 0.0224

B - 0.0400

STANDARD CURVE FOR ONDANSETRON HCL

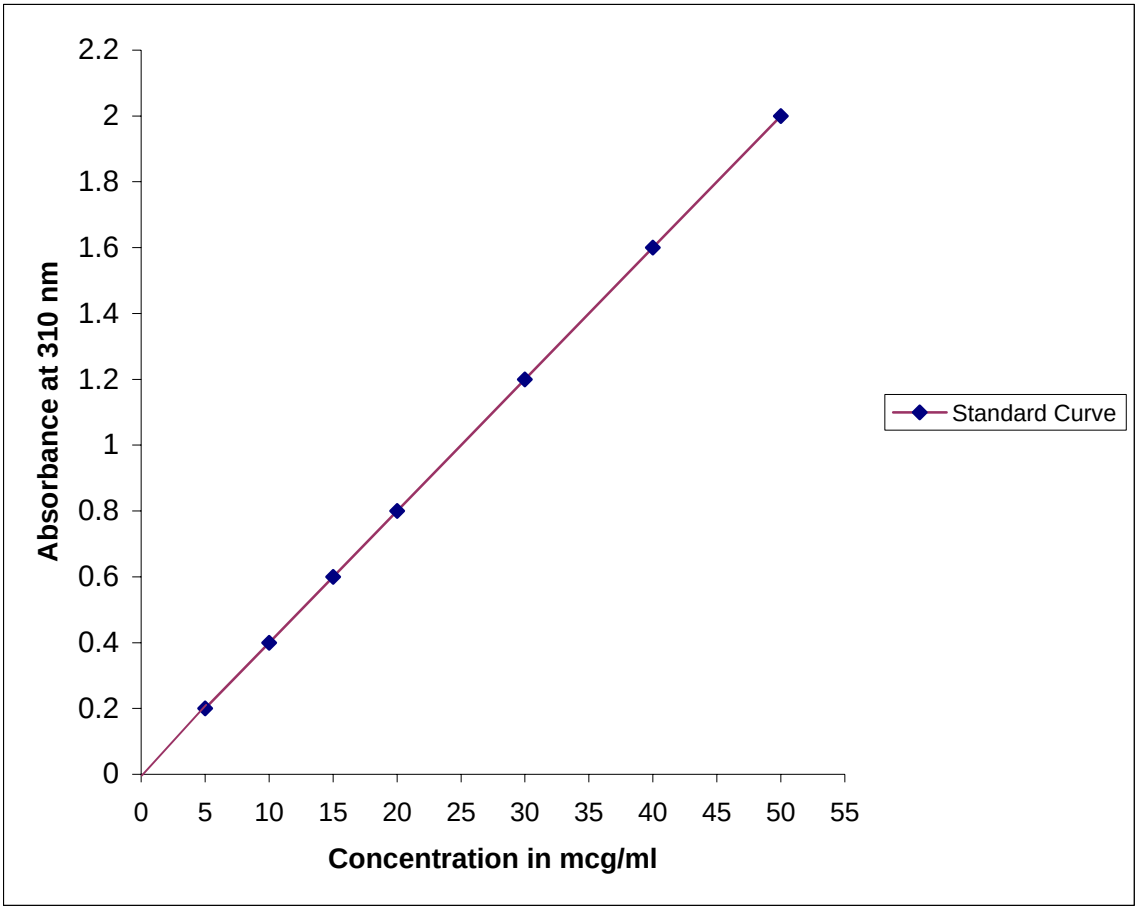


Table-13

RATIO / CONCENTRATION OF POLYMER USED TO THE DRUG

Sr. No	Batch number	Drug-polymer ratio
1	F-I (HPMC K 4 M)	1:2
2	F-I (HPMC K 4 M)	1:3
3	F-II (HPMC K 15 M)	1:2
4	F-IV (HPMC K 15 M)	1:3
5	F-V(HPMC K 100 LVP)	1:2

PREPARATION OF ONDANSETRON HYDROCHLORIDE SR TABLETS.

Granulation

Ondansetron Hydro chloride SR tablets was prepared by using wet granulation technique. Granulation is the process in which powder particles are made to adhere to form larger particles called granules. Granulation will commerce after mixing the necessary powdered ingredients, so that a uniform distribution of each ingredient through the mix is achieved.

Reasons for granulation:

- To prevent segregation of constituents in the powder mixture.
- To improve the flow properties of the mixture.
- To improve the compression characteristics of the mixture.
- Granules being denser than the parent powder mixture, occupy less volume per unit weight. They are therefore more convenient for storage.

Procedure:

1) Ondansetron Hydrochloride, lactose, avicel PH 101, first portion of HPMC K 100 LVP were passed through 40 mesh.

2) Binding solution was prepared with water. It was added to step I and granulate them.

3) Wet granules were passed through 12 mesh & dried for some times.

4) Dried granules were through 20 mesh and prelubricated with rest of the portion of HPMC K 100 LVP .

5) Prelubricated granules were lubricated with aerosol, talc which was already passed trough 40 mesh.6) Blend well for 30 minutes.7)Compress the blend into tablet using tablet compression machine.

Coating of the tablet:

Tablet coating is the application of coating composition to moving bed of tablets with concurrent use of heated air to facilitate evaporation of solvent.

Basis principles involve

i) Insulation which influences the release pattern as little as possible and does not markedly changed the appearance.

ii) Modified release with specific requirement and release mechanism adapted to body function in the digestive tract.

iii) Colour coating which provides insulation or is combined with modified release coating.

Procedure:

1) IPA was stirred in a colloidal mill and titanium dioxide was added slowly, avoiding powder floatation on the liquid surface.

2) Methylene chloride was added and mixed well for thirty minutes to get uniform dispersion .

3) Finally the above dispersion was passed through 200 mesh nylon cloth.

4) The core tablets were coated in the coating pan.

Preformulation studies

Angle of repose

With care, dynamic angle of repose measurement can be replicated with relative standard deviation of approximately 2 % they are particularly sensitive to change in particle size distribution and to moisture content and they provide rapid means of monitoring significant batch difference in these respells.

$$\theta = \tan^{-1} h/r$$

Where,

θ - Angle of repose

H-Height of the pile

R-Radius of the base of the conical pile

Angle of repose was determined by using funnel method. Powder was paired from a funnel that can be raised vertically until a maximum cone heights, it was obtained. Diameter of heap, d was measured.

The angle of respose calculated by above formula

Table-14

Angle of Respose as indicating of powder flow-properties

Angle of repose (Degrees)	Types or flow
<20	Excellent
20-30	Good
30-34	Passable
> 40	Very poor

Bulk Density

Bulk density is of great importance when one considers the size of high dose capsule product (or) me homogeneity of how dose formulation in which where is large difference in drug and Excipients densities. Apparent bulk density is determined by pouring pre sieved (40 sieve) bulk drug into a graduated cylinder via a large and measuring the volume and weight “as it as”.

Powder flow properties

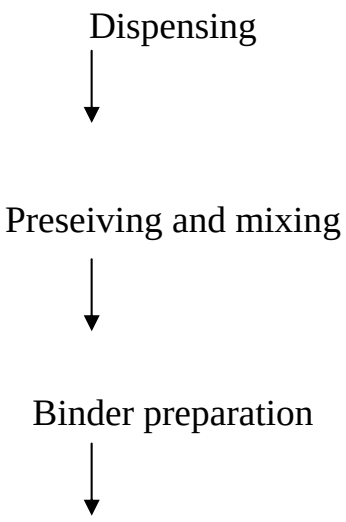
One of the ways of measurement of free flowing ability of powder is compressibility.

Carr’s indes = (Vi – Vt) /Vi X 100

Vi = Tapped density

Vt = Initial bulk density

Process flow chart



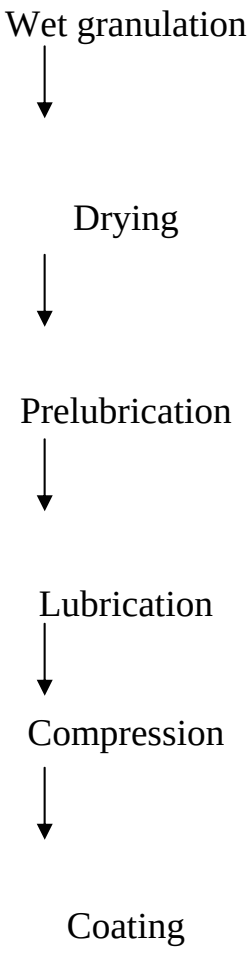

Wet granulation
Drying
Prelubrication
Lubrication
Compression
Coating

Table-15

COMPOSITION OF SUSTAINED RELEASE TABLETS OF ONDANSETRON HYDROCHLORIDE

I. FOR CORE TABLET

Batch ingredients	F-I (mg)	F-II (mg)	F-III (mg)	F-IV (mg)	F-V (mg)
Ondansetron HCl	5.02	5.02	5.02	5.02	5.02
Lactose Monohydrate	47.19	43.39	47.19	43.39	47.19
Microcrystalline Cellulose (Avicel PH 101)	18.3	16.83	18.3	16.83	18.3
Starch	7.5	7.5	7.5	7.5	7.5
Purified Water	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	0.5	0.5	0.5	0.5	0.5
HPMC K 4 M	10.04	15.06	-	-	-
HPMC K 15 M	-	-	10.04	15.06	-
HPMC K 100 LVP	-	-	-	-	10.04
Aerosil	0.3	0.3	0.3	0.3	0.3

Table-16

II. Composition of coating suspension

Batch ingredients	(mg)
HPMC 15 cps	1.230
Dibutyl Phthalate	0.015
PEG 6000	0.055
Talc	0.55
Titanium Dioxide	0.200
Dichloromethane	q.s
Isopropyl alcohol	q.s

Evaluation of tablets

Weight variation

Weight of 20 tablets was determined. From that average weight was calculated. Then individual tablet were weighed and the individual weight was compared with the average weight.

Table-16

Specification as BP

S.No	Average weight of the Tablets	Percentage deviation
1	80 mg or less	10
2	More than 80 mg but less than 250 mg	7.5
3	250 mg or more	5

Hardness

Although there is no official test for tablet hardness this property must be controlled during production to ensure that the product is firm enough to withstand handling without breaking, chipping etc., the hardness of a tablet is indicative of its tensile strength and is measured in term of pressure required to crush it when placed on its edge. Hardness of about 5 kg/cm^2 is considered to be minimum for uncoated tablets for mechanical stability. The hardness had influence on disintegration and dissolution times. Hardness is the factor that affects the bioavailability.

Friability

Friability generally refers to loss in weight of tablets in the container due to chapping, abrasion, and erosion. The standard device available is “Friabilators” (Consist of circular plastic chamber, a divide into two compartments. The chamber rotates at a speed of 25 r.p.m and drops tablets by distance of 15 cm). the weight loss should not be more than one percent.

Formula

Percentage Friability = (initial weight – final weight / initial weight) X 100

Procedure

10 tablets are weighed and transferred in to Friabilator. Then after 100 revolutions per minute the tablets were unloaded and weight of the tablets was noted. The difference should not exceed one percent.

Disintegration time

Tablet was added to 100 ml distilled water at 37^0c± 0.5 ^{0}C. Time required for complete dispersion of a tablet was measured win help of digital tablet disintegration test apparatus.

Uniformity of content

Procedure

Crush two tablets, taken the powder equivalent of dose 10mg, add 100 ml water. take 0.5ml and diluted with water.The measure the absorbance of resulting solution at 310 mm using UV- spectro photometrically.

ACCELERATED STABILITY STUDIES

Stability

Stability is officially defined as the time lapse during which the drug product retains the same properties and characteristics that it possessed at the time of manufacture. This process begins at early devolvement phases.

Instability in modern formulation is often detectable only after considerable storage period under normal condition. To assess the stability of a formulated product its usual to expose it to high stress conditions to enhance its detoriation and therefore the time required for testing is reduce common high stress like temperature and humidity. This will eliminate unsatisfactory formulation.

Strategy of stability testing

1. The study of drug decomposition kinetics
2. The development of stability dosage form.
3. Establishment of expiration date for commercially available drug product is some of the needs of stability testing.
4. Data form stability studies should be provided on at least there primary batches of the drug product.
5. The batches should be manufactured to a minimum of pilot scale.
6. Important point of view of the safety of the patient, patient relieves a uniform dose of drug throughout the shelf life of the product.

Table-18

The Stability Storage Condition

S.No	Study	Storage condition	Minimum period
1.	Long-term study	25^0 C±2^0C 60 % ±5% RH	12 month
2	Intermediate study	30^0 C±2^0C 65 % ±5% RH	6 month
3	Accelerated study	40^0 C±2^0C 75 % ±5% RH	6 month

Procedure

Selected batches were placed in a high density polyethylene container, blister pack, strip pack etc. They are kept in stability chamber maintained at 40^0 C & 75 % RH. The stability studies were carried out for a period of one month. The tablets were tested and checked for the above mention specification.

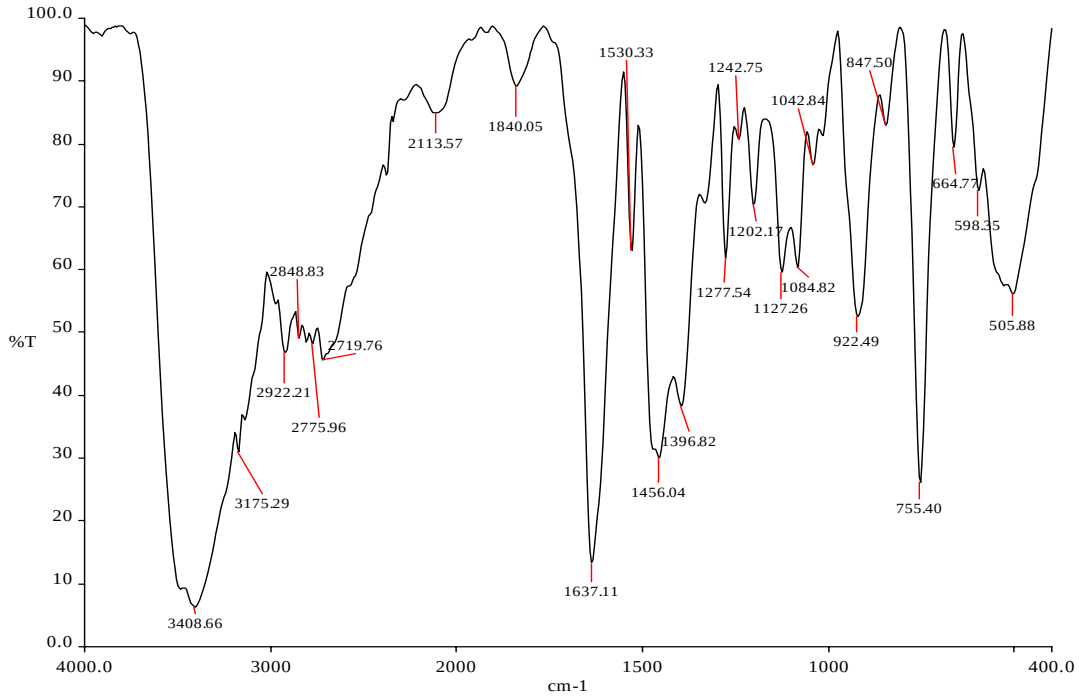
8. Results and Discussion

Figure. No. 5 IR Spectrum of ondansetron hydrochloride

ACIC
St.Joseph's College (Autonomous)
Trichy-2

FTIR SPECTRUM
Date: 4/19/2008

Spectrum Name: Sam=Ondansetronhcl.sp



Sam=Ondansetronhcl.pk

SAM_ON~1.SP 3601 4000.00 400.00 6.37 98.89 4.00 %T 3 2.00

REF 4000 98.89 2000 93.79 600
3408.66 6.37 3175.29 31.07 2922.21 46.79 2848.83 49.02 2775.96 48.30
2719.76 45.57 2113.57 84.89 1840.05 89.29 1637.11 13.28 1530.33 63.15
1456.04 30.11 1396.82 38.26 1277.54 61.91 1242.75 80.63 1202.17 70.33
1127.26 59.56 1084.82 60.47 1042.84 76.57 922.49 52.55 847.50 82.91
755.40 26.17 664.77 79.46 598.35 72.69 505.88 56.19

Table No. 17

IR Spectrum of ondansetron hydrochloride

Sr. No	Wave number	Functional group
1.	1637.4	N = N stretching
2.	755.40	CH bending aromatic
3.	2848.83 2719.76	Two distinct peaks methyl group
4.	3408.06	NH stretching
5.	1840.5	C = o stretching

Discussion
IR spectrum was confirmed by ondansetron HCl

Table No. 17

Active pharmaceutical Coonsideration

Powder Properties of Formulation

Sr. No	Formulation code	*Bulk Density(gm/ml)	*Angle of Repose	Carr's index %
1	F-I	0.333	$21^0 41'$	15.62
2	F-II	0.348	$21^0 43'$	11.90
3	F-III	0.375	$21^0 20'$	12.12
4	F-IV	0.352	$24^0 09'$	14.02
5	F-V	0.344	$20^0 10'$	15.62

***Average value of three observations.**

Discussion

The value of angle of respose and Carr's index less than 25^0 and 15 % respectively, hence the flow properties all formulations complied within the limits.

Dissolution Condition

Apparatus	:	USP Type – II (Paddle)
Speed	:	75 rpm
Time	:	1,4,8, and 12
Dissolution medium	:	0.1 N HCL
Qty. of Dissolution medium	:	900 ml
Temperature	:	$37^0C\pm 0.5^0C$

Preparation of 0.1 NHCL

Weight and transfer accurately about 55.37 mg of Ondasetron HCl (44.4mg of Tizanidine) working standard into a 100 ml volumetric flash, add 70ml of methanol, sonicate for 5-10 and and make a volume with methano. (conce 444.44 mcg /ml)

From this solution take 5 ml into 50 ml volumetric flask volume make up by using dissolution medium (conc, 44.044 mgc/ml)

From this solution take 5 ml into 50ml volumetric flask volume make by using 0.1N HCL.(conc.4.44 mcg/ml)

From this solution take 5 ml into 10ml volumetric flask volume make by using mobile phase. (conc. 2.22 mcg/ml)

Chromatographic conditions

Column : Lichroshere, CN, 250x 4.6mm, 5 micrometer

Wavelength : 247 nm

Flow rate : 1.0ml /min

Injection volume : 50 Microlitres

Runtime : 15 min

Table No. 18

System suitability

Parameter	Limit	results
Theratica plate	NLT 850	4542.92
Assmetry	NMT	2 0. 9
Capacity factor	NLT	2 2.5.

Table No. 19

PHYSICAL PARAMETERS OF FABRICATED TABLETS

(n=20)

Sr.No	Formulations	Average Tablet Weight (mg)	Hardness (Kg/cm)	Thickness (mm)	Diameter (mm)	Friability (%)
1	F-I	91.13	4.9	2.53	5.92	0.54
2	F-II	91.12	4.9	2.52	5.92	0.53
3	F-III	91.32	4.9	2.52	5.92	0.56
4	F-IV	90.57	4.9	2.52	5.92	0.52
5	F-V	91.35	5.0	2.53	5.92	0.50

Table No. 20

CUMULATIVE PERCENT RELEASED OF ONDANSETRON HYDROCHLORIDE FROM FABRICATED SR MATRIX TABLETS F-I TO F-V IN pH 6.8 PHOSPHATE BUFFER

Time in Hours	F-I	F-II	F-III	F-IV	F-V
1	29.5	25.9	28.6	28.4	20.4
4	72.8	68.4	85.6	70.7	36.3
8	102.2	101.4	85.6	98.4	72.4
12	104.4	103.4	99.4	100.8	100.21

Table No. 21

ASSAY OF FABRICATED FORMULATION

Sr. No	Formulation	% of ondansetron
1	F-I	99.73
2	F-II	99.85
3	F-III	98.26
4	F-IV	98.92
5	F-V	100.23

Table No. 22

IN VITRO RELEASE PROFILE OF F-V TABLET KEPT AFTER STORAGE AT 40^0C & 75% RH, ROOM TEMPERATURE FOR 30 DAYS.

Time Interval (hrs)	Batch Number	
	Percentage drug release	
	F-V	
	Initial	After 30 Days
1	20.4	20.8
4	50.1	50.7
8	72.4	72.6
12	100.21	100.23
Assay (%)	100.23	100.15

Figure. No. 6 ONDANSETRON INVITRO RELEASE CURVE OF FORMULATION F-1

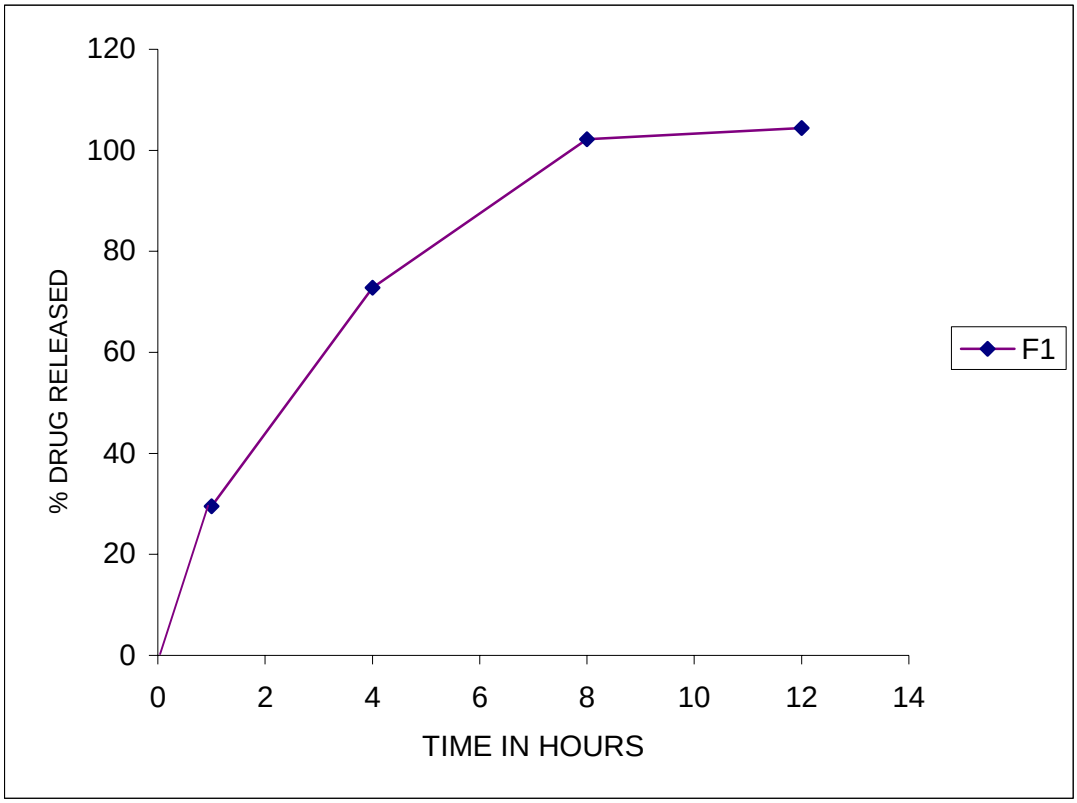


Figure. No. 7 ONDANSETRON INVITRO RELEASE CURVE OF FORMULATION F-2

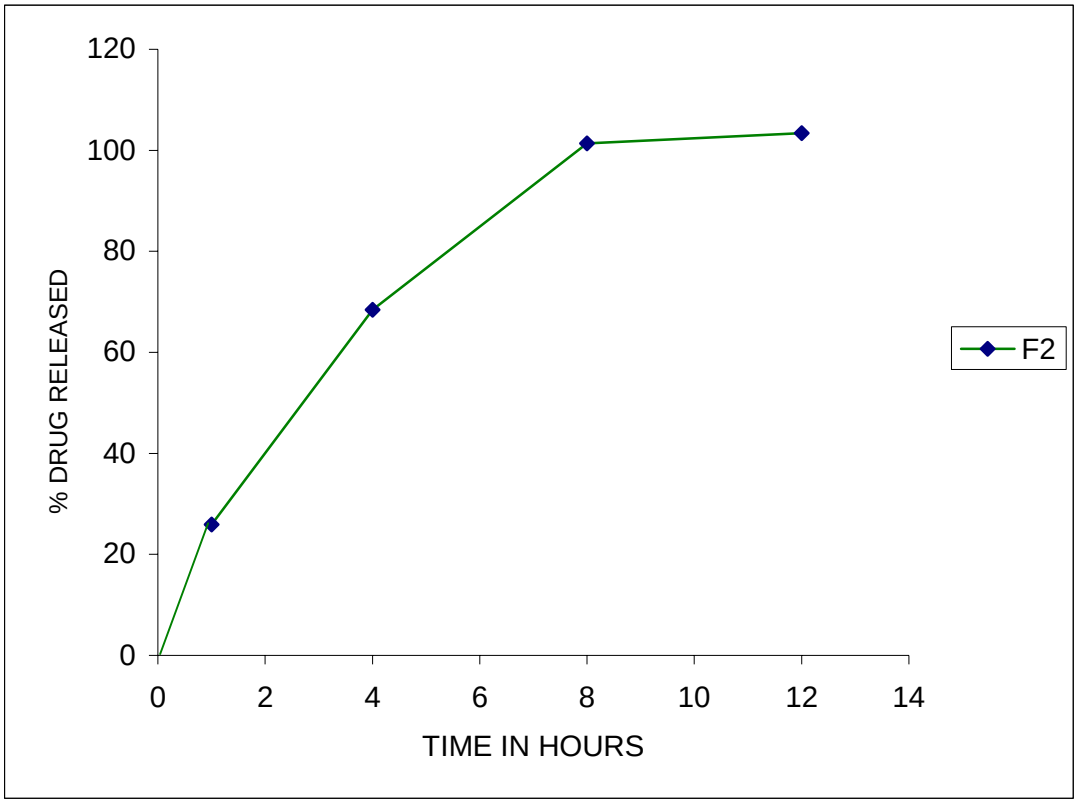


Figure. No. 9 ONDANSETRON INVITRO RELEASE CURVE OF FORMULATION F-3

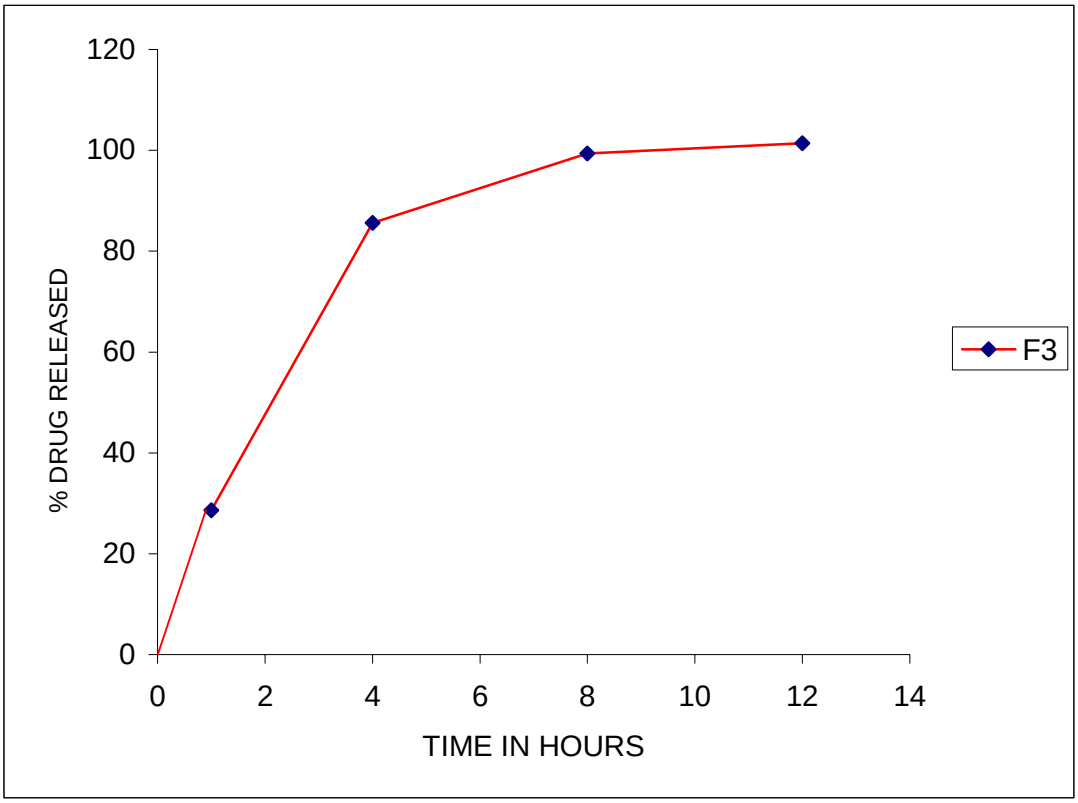


Figure. No. 10 ONDANSETRON INVITRO RELEASE CURVE OF FORMULATION F-4

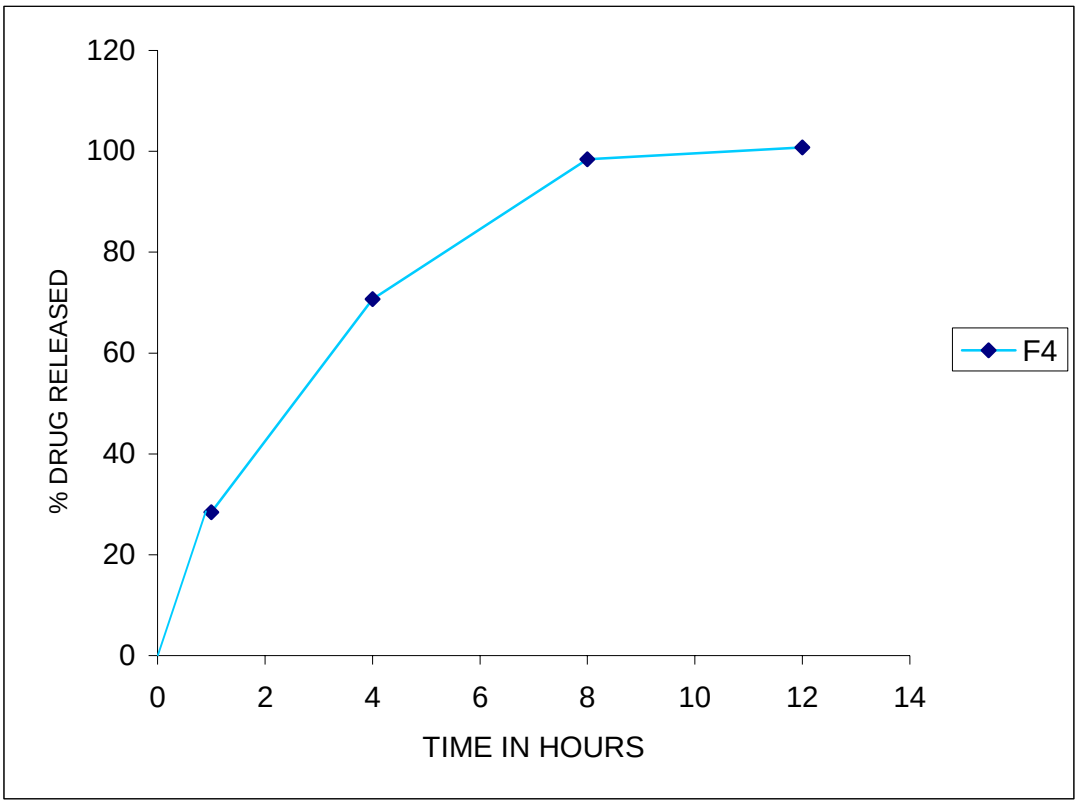


Figure. No. 11 ONDANSETRON INVITRO RELEASE CURVE OF FORMULATION F-5

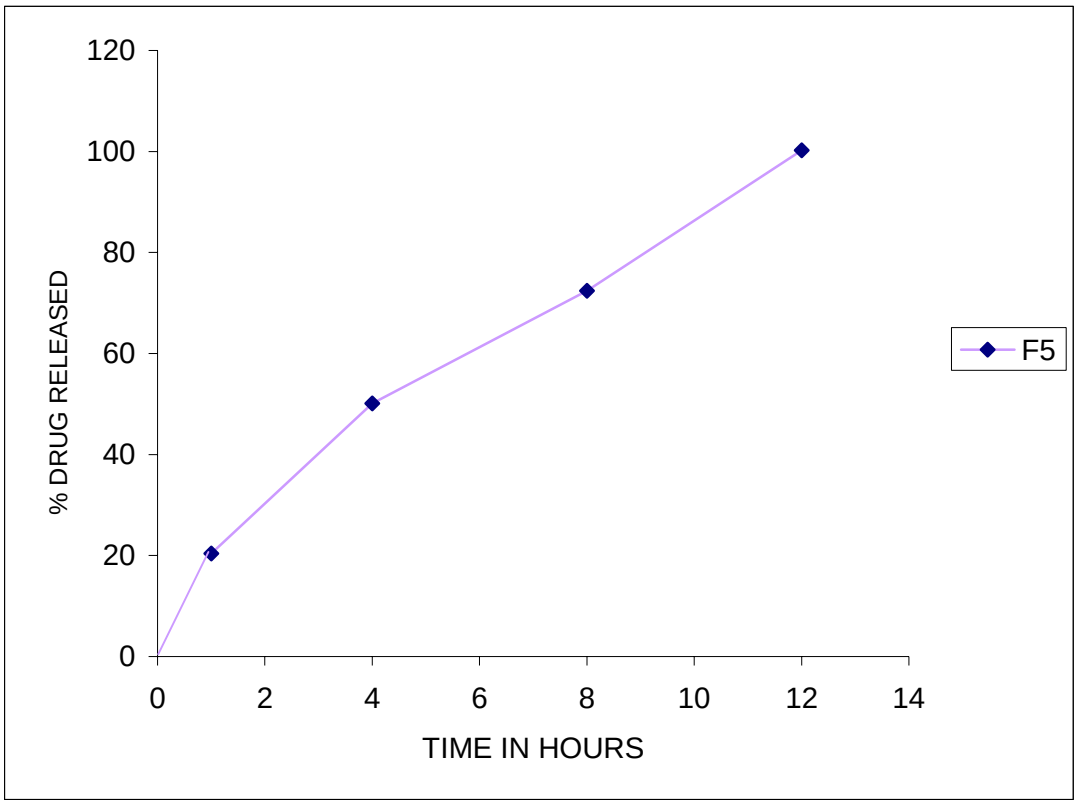


Figure. No. 12 ONDANSETRON INVITRO RELEASE CURVE OF FORMULATION F-5 STABILITY BATCH

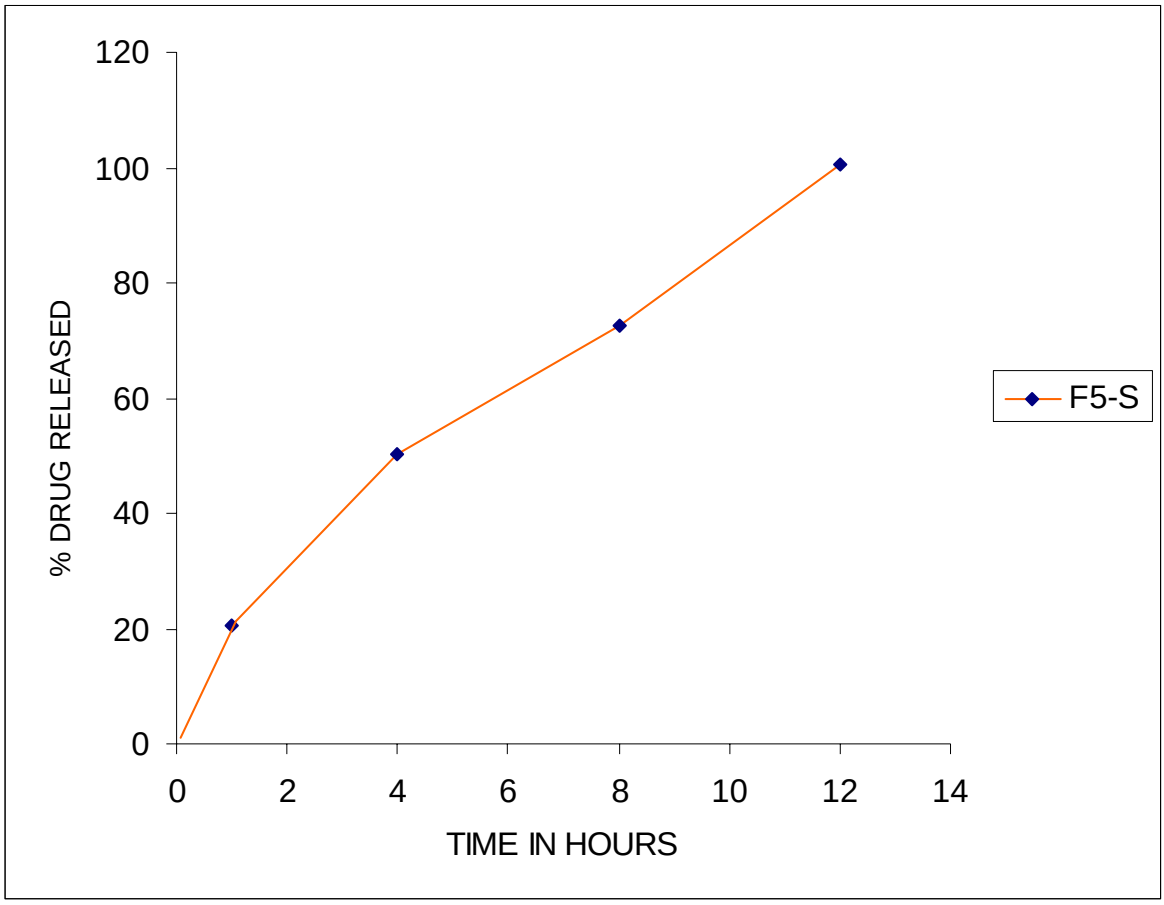


Figure. No. 13 COMPARATIVE IN VITRO DRUG RELEASE FOR F1, F2 , F3, F4, F5

9. Summary and Conclusion

- The present work is to develop a formulation with ondansetron

Hydro chloride as a sustained Release tablet dosage from for the treatment of cancer Chemotherapy in nausea and vomiting.

- Under, this, drug characterization and drug excipients interaction studies were carried out. The drug characterization showed satisfactory results.
- The physico chemical properties of the finished Poduct is complies with specifications.
- Ondansetron Hydrochloride SR tablets are formulated by using HPMC polymers in different concentrations.
- Five different formulations are formulated and evaluated.
- Only formulation five is better sustained release than compare with other formulation.
- Formulation five gives a release of 100.23 for an 12 hours.
- The prepared formulations are stable at or below 40^0C, hence it can be easily stored at room tempetature.
- This work concluding that has achieved the objectives of sustained release up to 12 hours.

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