CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF METAPROLOL SUCCINATE

Mr.K.Tharun Kumar*, R.Aravind[1], Dr.T.Mangilal [2]

*As an Executive In Department of Quality Assurance, Natco Pharma Limited Formulation Division, Kothur, Rangareddy-508228, Telangana, India.

[1] As an Executive In Department of Production, Natco Pharma Limited Formulation Division, Kothur, Rangareddy-508228, Telangana, India.

[2] Professor and of the Department, Department of Pharmaceutics , Geethanjali College of Pharmacy, Cheeryal, Keesara, Rangareddy-501301,Telanga,India.

Abstract:

Metoprolol succinate is a selective beta adrenergic receptor blocker useful in treatment of hypertension, angina & heart failure. the objective of the present study was to develop sustained release matrix tablets of Metaprolol succinate by using different polymers like hydrophobic polymers ethyl cellulose hpmck15. Herehydroxy propyl methyle cellulose was used to control burst release. the tablets were prepared by direct compression method. the compressed matrix tablets were evaluated for various parameters like Hardness, Friability, Weight variations, drug polymer interaction and in-vitro drug release studies. In-vitro drug release studies were performed in ph6.8 phosphate buffer using usp type 2 (paddle type) at 50 rpm for 12hours.

Key Words: *Metoprolol succinate, Beta adrenergic receptor blocker, Treatment of hypertension, Angina Pectoris.*

Corresponding Author: Mr. K. Tharun Kumar, *As an Executive In Department of Quality Assurance, Natco Pharma Limited Formulation Division, Kothur, Rangareddy-508228, Telangana, India.*

Corresponding Author:

K.Tharun Kumar,

As an Executive In Department of Quality Assurance, Natco Pharma Limited Formulation Division, Kothur, Rangareddy-508228, Telangana, India.

QR code

Please cite this article in press as K.Tharun Kumar et al., ***Formulation And Evaluation Of Sustained Release Matrix Tablets Of Metaprolol Succinate****, Indo Am. J. P. Sci, 2017; 4(11).*

INTRODUCTION:

An ideal drug delivery system should be able to deliver an adequate amount of drug, preferably for an extended period of time, for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body, and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such problems, controlled release and sustained release delivery are receiving considerable attention from pharmaceutical industries worldwide. Despite presence of varied routes of drug administration, oral route remains the preferred route of choice. This route provides maximum patient compliance, is relatively simple to formulate for the formulator and convenient for the patient to administer. Particularly oral controlled release formulation, which releases active ingredient over an extended period as opposed to the administration of a number of single doses at regular intervals, has long been recognized in the pharmaceutical art.[1]

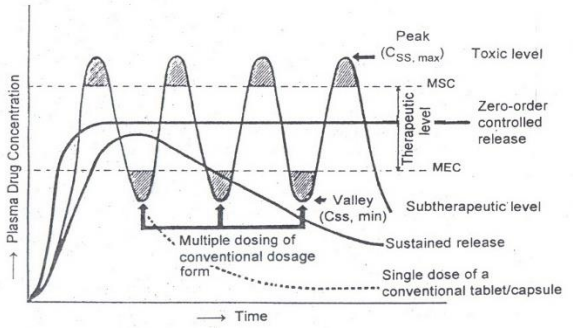
Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting.

The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery.

When a conventional dosage form is administered, the concentration of drug in the blood stream will attain a "therapeutic range" necessary for the action of the drug. This therapeutic range would be maintained for some time and finally the concentration drops below this range rendering the drug therapeutically inactive. An ideal drug delivery system involves two prerequisites. It should deliver the drug at a rate desired by the needs of the body and over the period of treatment.

This necessitates steady state blood levels or tissue levels that are therapeutically effective and nontoxic for an extended period of time. It should channel the active entity to the site of action.

Advanced research in pharmaceutical technology would find several controlled release dosage forms in the market. These products have been identified by various names as "sustained release", "prolonged release", "controlled release", "timed release", and "delayed release".[2]



A hypothetical plasma concentration-time profile from conventional, multiple dosing and single doses of sustained and controlled delivery formulations.

Terminology

In the past, many of the terms used to refer to therapeutic systems of controlled and sustained release have been used in an inconsistent and confusing manner. Although descriptive terms such as "timed release" and "prolonged release" give excellent manufacturer identification, they can be confusing to health care professionals. Several descriptions have been given to sustained and controlled release.

R. Robinson defined **sustained release** as "Any dosage form that provide medication over an extended time" and controlled release as "Any dosage form which is able to provide some actual therapeutic control, whether this can be of temporal nature, spatial nature, or both". In other words, controlled release system attempts to control drug concentrations in the target tissue. This correctly suggests that there are sustained release systems that cannot be considered controlled release systems.

The terminologies, which are frequently used in practice, are given below:[3]

- Zero-order release
- Sustained release
- Controlled release
- Extended release (Prolonged release)
- Repeat action tablets
- Delayed-release systems

In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually achieved by attempting to obtain **zero-order release** from the dosage form. Zero-order release constitutes drug release from the dosage that is independent of the amount of drug in the delivery system.

Sustained release systems generally do not attain this type of release and usually try to mimic zero-order

release by providing drug in a slow first order fashion. Systems that are designated as prolonged release can also be considered as attempts at achieving sustained release delivery. Repeat action tablets are an alternative method of sustained release in which multiple doses of a drug are contained within a dosage form, and each dose is released at periodic interval. Delayed release systems, in contrast, may not be sustaining, since often the function of these dosage form is to maintain the drug within the dosage form for some time before release. Commonly, the release rate of drug is not altered and does not result in sustained delivery once drug release has begun. Enteric coating tablets are an example of this type of dosage form.

Controlled release, although resulting in a zero order delivery system, may also incorporate methods to promote localization of the drug at an active site. In some cases, a controlled release system will not be sustaining, but will be concerned strictly with localization of the drug. Site specific systems and targeted delivery systems are the descriptive terms used to denote this type of delivery control (Gwen *et al*., 2002).

The ideal of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems. This approximation is achieved by creating a constant concentration in the body or an organ over an extended time; in other words, the amount of drug entering the system is equivalent to the amount removed from the system.

All forms of metabolism and excretion are included in the removal process; urinary excretion, enterohepatic recycling, sweat, fecal, and so on. Since for most drugs, these elimination processes are first order, it can be said that at a certain blood level, the drug will have a specific rate of elimination (Y. W. Chien, 1992). The idea is to deliver the drug at this exact rate for an extended period. This is represented mathematically as:

$$\text{Rate in} = \text{Rate out} = K_{elim} * C_d *$$

Where C_d is defined as desired drug level, $V_d$is the volume of distribution, and k_{elim} is the rate constant for drug elimination from the body. Often such exacting delivery rates prove to be difficult to achieve by administration routes other than intravenous infusion. Non-invasive routes (e.g., oral) are obviously preferred.

The goal of controlled release systems is to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets, the drug level in the blood follows the profile shown in figure 1.1 in which level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent toxic level, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long term administration the drug level in the blood follow the profile shown in figure 1.1 remaining constant, between the desired maximum and minimum, for an extended period of time.[4]

Advantages of sustained release formulations

Extended release formulations have many advantages over traditional, immediate release products.

- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady-state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of dose administered.
- Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

Disadvantages of sustained release formulations

- Decreased systemic availability in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site-specific absorption, pH-dependent solubility, etc.
- Poor *in vitro-in vivo* correlation.
- Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

- Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
- Higher cost of formulation.

Factors influencing the design and performance of sustained release

Products

The type of delivery system and route of administration of the drug presented in sustained drug delivery system may depend upon two properties. They are:

I. Physicochemical properties of drugs
II. Biological factors.

I. Physicochemical Properties of Drugs [5]

1. Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general a single dose of 0.5 to 1gm is considered maximum (Nicholas *et al*., 1987).

2. Ionization, pKa & Aqueous Solubility

The pH Partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues. Therefore it is important to note the relationship between theP^{Ka} of the compound and its absorptive environment. For many compounds, the site of maximum absorption will also be the area in which the drug is least soluble (Gwen *et al*., 2002).

3. Partition coefficient

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability (Salzman NP *et al*., 1972). Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes.

Drug Stability

The drugs, which are unstable in stomach, can be placed in a slowly soluble form and their release delayed until they reach the small intestine. However, such a strategy would be detrimental for drugs that either are unstable in the small intestine (or) undergo extensive gut wall metabolism, as pointed out in the decrease bioavailability of some anticholinergic drugs from controlled /sustained release formulation.

Biological Factors [6]

Pharmacokinetic Characteristics of the Drug

1. Biological Half-Life

Therapeutic compounds with half-life less than 8 hrs are excellent candidates for sustained and extended release preparations. Drugs with very short half-life (less than 2 hrs) will require excessively large amounts of drug in each dosage unit to maintain controlled effects. Thus forcing the dosage form itself to become too large to be administered. Compounds with relatively long half-lives, generally greater than 8 hrs are not used in the extended release dosage forms, since their effect is already sustained and also GI transit time is 8-12 hrs (Jantzen GM *et al*., 1996). So the drugs, which have long -half life and short half- life, are poor candidates for sustained release dosage forms.

Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Drugs which are absorbed by specialized transport process (carrier mediated) and drug absorption at special sites of the gastrointestinal tract (Absorption Window) are poor candidates for extended release products (Gwen *et al*., 2002).

Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constant(s) for the process (es) are not too large, successful sustained-release products can be developed.

There are two factors associated with the metabolism of some drugs; however that present problems of their use in sustained-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Pharmacodynamic Characteristics of the Drug [7]

1. Therapeutic Range

A drug candidate for controlled delivery system should have a therapeutic range wide enough such that variations in the release rate do not result in a concentration beyond this level.

2. Therapeutic Index (TI)

The release rate of a drug with narrow therapeutic index should be such that the plasma concentration attained is within the therapeutically safe and effective range. This is necessary because such drugs have toxic concentration nearer to their therapeutic range. Precise control of release rate of a potent drug with narrow margin of safety is difficult. A drug with short half-life and narrow therapeutic index should be administered more frequently than twice a day. One must also consider the activity of drug metabolites since controlled delivery system controls only the release of parent drug but not its metabolism.

Plasma Concentration-Response Relationship: Drugs such as reserpine whose pharmacological

activity is independent of its concentration are poor candidates for controlled release systems (Gwen *et al*., 2002).

Polymers used in Sustained release Formulations:

Polymers have gained importance in pharmaceutical industry as both drug encapsulants and vehicles of drug carriage; either protecting an active agent during its passage through the body until its release, or controlling its release. Polymers in drug delivery are classified into:

Bio-degradable polymers: [8]

- Natural: Alginates, Guar gum, Chitosan, Gelatin, Xanthan gum and Carrageenan.
- Synthetic: Polylactic acid, Polycaprolactone, Polyglycolic acid, Poly lactic- glycolic acid and Polyanhydride.

Bio-absorbable polymer: Polyethylene glycol and polyvinylpyrrolidone

Non-Biodegradable polymers: Hydroxy propyl methyl cellulose, ethyl- cellulose, Acrylic Polymers, Silicone elastomers, Poly vinyl chloride, Polyurethanes and polyethyl/vinyl acetate polymers.

The greatest advantage of biodegradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials do produce degradation by products that must be tolerated with little or no adverse reactions within the biological environment (Vyas and Khar, 2006).

Oral Drug Delivery Systems [9]

Total 5 types of oral controlled release systems are available, classified based on the release mechanism: -

1.Dissolution controlled release system.
2.Diffusion controlled release system.
3.Biodegradable and combination diffusion and dissolution systems.
4.Osmotic ally controlled release systems.
5.Ion exchange systems.

Dissolution controlled release system

A drug with a slow dissolution rate will sustain release rate of the drug from the dosage form. Here the rate-limiting step is dissolution. This being true, decreasing their rate of dissolution could make sustained release preparation of drugs. These approaches are achieved by preparing appropriate salts or derivatives, coating the drug with a slow dissolving material or incorporating it into a tablet with a slowly dissolving carrier.

Dissolution controlled systems can be made either by rate controlling coats or by administering the drug as a group of beads that have coating of different thickness. In first case if the outer layer is a quickly releasing bolus of drug, initial levels of drug in the body can be quickly established with pulsed intervals. In second case since the beads have different coating thickness, their release will occur in a progressive manner. Those with the thinnest layer will provide the initial dose and the maintenance of drug levels at later times will be achieved from those with thicker coating.

This dissolution process at steady state is described by the Noyes-Whitney equation.

$$\frac{dc}{dt} = K_D A (C_s - C) = \frac{D}{h} A (C_s - C)$$

Where,

dc/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

The above equation predicts that the rate of release can be constant only if the following parameters are constant.

a) Surface area
b) Diffusion coefficient
c) Diffusion layer thickness
d) Concentration difference

But these parameters are not easily maintained constant, especially surface area. For spherical particles, the change in surface area can be related to the weight of the particle, which is under assumption of sink conditions, above equation can be rewritten as the cube root dissolution equation.

$$W_0^{1/3} - W^{1/3} = K_D t$$

Where,

K_D = Cube root dissolution rate constant
W_0 = Initial weight
W = Weight of the amount remaining at time t.

Diffusion controlled release system [10]

In this system, release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. It may be:

a) Réservoir devices
b) Matrix device

a)**Réservoir devices**

c) Reservoir devices are characterized by a core of drug, the reservoir, surrounded by a polymeric

membrane. The nature of the membrane determines the rate of release of drug from the system.

d) The process of diffusion is described by Fick's equation. This equation states that the amount of drug passing across a unit area is proportional to the concentration difference across that plane.

e) The equation is given as **J = -D dc/dx** …….(1)

f) Where,

g) J = given in units of amount/ area-time,

h) D = is the diffusion coefficient of the drug in the membrane (Area/time).

i) dc/dx = represents the rate of change in concentration 'C' relative to a distance 'X' in the membrane.

j) Equation (1) can be integrated and simplified to give, **J= DK△C/ d.** ……(2)

k) Where,

l) K = Partition coefficient

m) △C = Concentration difference across the membrane.

n) D = Thickness of the diffusion layer.

o) In the equation (2) it is assumed that 'D' and 'K' are constant.

p) Drug release will vary, depending on the geometry of the system. The simplest system to consider is that of a slab, where drug release is from only one surface. In this case equation (2) can be written as

q) $\frac{DMt}{DT} = \frac{ADK\triangle C}{d}$ …… (3)

r) Where,

s) Mt is the mass of drug released after time 't',

t) DMt /dt the steady-state release rate at time 't'

u) 'A' the surface area of the device.

The left side of equation (3) represents the release rate of the system. A true controlled release system with a zero- order release rate can be possible if all of the variables on the right side of equation (3) remain constant. But it is very difficult to maintain all the parameters constant. Again depending on the device diffusion systems can provide constant release at steady state. For reservoir devices, a system that is used relatively soon after construction will demonstrate a large time in release, since it will take time for the drug to diffuse from the reservoir to the membrane surface. On the other hand, systems that are stored will demonstrate a burst effect, since, on standing the membrane becomes saturated with available drug. The magnitude of these effects is

Matrix devices

Matrix devices consist of drug dispersed homogenously throughout a polymer matrix. 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 toward the interior. For this system, rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

. A pseudo steady state is maintained during drug release.

a. The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.

b. The bathing solution provides sink conditions at all times.

c. The diffusion coefficient of drug in the matrix remains constant i.e. no change occurs in the characteristics of the polymer matrix.

d. The rate of release of drugs dispersed in an inert matrix system, have been derived by Higuchi

MATERIALS AND METHODS:

Various excipients selected for the study

S.NO	Name of the drug &excipient	Category
1	Metaprolol succinate	API
2	Microcrystalline cellulose	Diluent
3	Hydroxy propyl methyl cellulose K4	Rate controlling Polymer
4	Ethyl Cellulose	Rate controlling Polymer
5	Talc	Glidant
6	Megnesium stearate	Lubricant

Preformulation Study of Drug [11-15]

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Determination of bulk density and tapped density: An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V0) was measured.

- Weigh the test sample and enter the weight of test sample to the instrument by pressing the enter key to resister the weight.
- Fill the test sample to be tested in to the measuring cylinder. Keep the measuring cylinder on to the cylinder holder, lock the holder assembly.
- Press the start key to run the instrument after tapping is over for 500 taps first measure the tap value.
- Ensure that the difference between two volumes is less than 2% than go for 3rd tapping up to 1250 taps.

Bulk density = W/ V0;

Tapped density = W/Vf

Where, W = weight of the powder V0 = initial volume Vf = final volume

Compressibility index (Carr's indices): Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material.

$$Ci = \frac{100\ (V0 - VF)}{V0}$$

Compressibility Index specifications

% Comp. Index	Properties
5-12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner Ratio: It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner Ratio = Tapped density / Bulk density

Hausner Ratio Specifications

Hausner Ratio	Property
0 - 1.2	Free flowing
1.2 – 1.6	Cohesive powder

Formulation

Formulation of Metaprolol succinate extended release tablets

INGREDIENTS	FORMULATIONS (mg)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Metaprolol succinate	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5
Ethyl cellulose	40	60	80	-	-	-	30	40	50
HPMC	-	-	-	50	60	70	50	40	30
Microcrystalline cellulose	97.5	77.5	57.5	87.5	77.5	67.5	57.5	57.5	57.5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Procedure

- **Weighing & Sifting:** Metaprolol succinate, and excipients are weighed and passed through 30 mesh.
- **Mixing:** Step 1 materials are mixed in a polybag.
- **Lubrication:** Megnesium Stearate and talc are passed through 40 mesh .They are added to the above and mixed.

Compression: The powder was compressed into tablets.

Evaluation of Metaprolol Sustained release Tablets

Size and Shape: The size and shape of tablets can be dimensionally described, monitored, and control. The compressed tablet's shape and dimensions are determined by the tooling during compression process.

Thickness: The thickness of a tablet was the only dimensional variable related to the process.10 tablets were measured for their thickness and diameter with vernier calipers. Average thickness and diameter were calculated.

Average weight: Weigh accurately 20 tablets and calculate the average weight.

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

Weight variation: The USP weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weighs to the average. The tablets met the UP test that there were no more than 2 tablets were outside the percentage limit and no tablet differed by more than 2 times the percentage limit.

Weight variation tolerances for uncoated tablets

S.No	Average Weight of tablets (mg)	Maximum percentage Difference Allowed
1	130 or Less	10
2	130 to 324	7.5
3	More than 324	5

Hardness: Hardness of the tablets was determined by breaking it between the second and third fingers with thumb being as a fulcrum. There was "sharp" snap, the tablet was deemed to have acceptable strength.
Hardness of the tablets is also determined by Stokes Monsanto hardness tester and the hardness should found within the range of 4-15 kg/cm².
Friability: The friability of tablets is determined by Roche fribilator 20 tablets were taken and weighed. After weighing the tablets were placed in the Roche friabilator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for 4 minutes dropping the tablets from a distance of six inches with each revolution. After operation the tablets were dedusted and reweighed.
Friability is determined by

$$F=100\ (1-W0/Wt)$$

Where,
W0 = Wt of tablets before friability test.
Wt = Wt of tablets after friability test.

***In-vitro* drug release studies**
Drug release was performed by using following conditions

Apparatus : USP Type 2 (paddle)

Agitation speed : 50 rpm

Medium : pH 6.8 , 900ml

Temperature : 37± 0.5^{0}C

Sampling interval : 1, 2, 4, 6, 8, 10, 12 hr

Wavelength : 222nm

Analysis of *in - vitro* drug Release kinetics: [16-20] To analyse the mechanism ofdrug release from table the dissolution data are fitted to four popular release model suchasa zero-order, first order, Higuchi and peppas equation .

i) Zero Order Kinetic.
It describes the system in which the drug release rate is independent of its concentration.
$Qt=Q_0+ K_0 t$

Where:Qt = Amount of drug dissolved in time t
Q_0 = Initial amount of drug in the solution, which is often zero and
K_0t = zero order release constant.

ii) First Order Kinetic.
It describes the drug release from the systems in which the release rate is concentration dependent.

$$\textbf{Log Qt = log } Q_0 \textbf{+ kt/ 2.303}$$

Where Qt = amount of drug released in time t.
Q_0 = initial amount of drug in the solution
k = first order releaseconstant
will be straight linewith a slope of kt/ 2.303 and an interceptat t=0 of log Q_0.

Higuchi Model.
It describes the fraction of drug release from a matrix is proportion at square root of time.

$$Q = K_2 t^{1/2};$$

Where,
Q = Amount of drug dissolved at time t
K_H = Higuchi dissolution constant reflection formulation characteristics.
If theHiguchi modelofdrugrelease(i.e.Fickiandiffusion)isobeyed,thenaplotof Qversust$^{1/2}$will be straight line with slope of k_H.

iv) Korsmeyer-Peppas model (Power Law): The release rate data was fitted the following equation

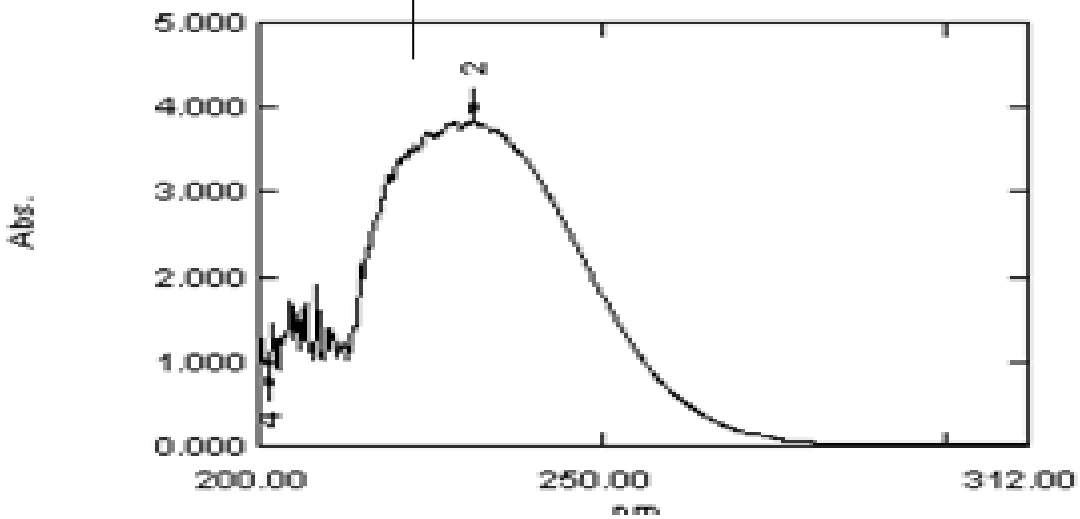
$$Mt / M\infty = Kt^n$$

Where

Mt and M∞ = fraction of drug release at time t,
k=release constant, t = release time, n=diffusionalreleaseexponent.
A plotoflog{Mt/M∞}versuslogtwillbelinearwithslopeofnandinterceptgives the value of log k.The 'n' (release exponent of Korsmeyer-Peppas model) value could be used to characterize different release mechanisms.
The interpretation of n values was done in the following table

N value	Release mechanism
n<0.5 (0.45)	quasi-Fickian Diffusion
n=0.5 (0.45)	Diffusion mechanism
0.5<n<1	Anomalous (non-Fickian) Diffusion
n=1 (0.89)	Case 2 transport (zero order release)
n>1 (0.89) -	Super Case 2 transport (relaxation)

Drug excipient compatability studies [21]



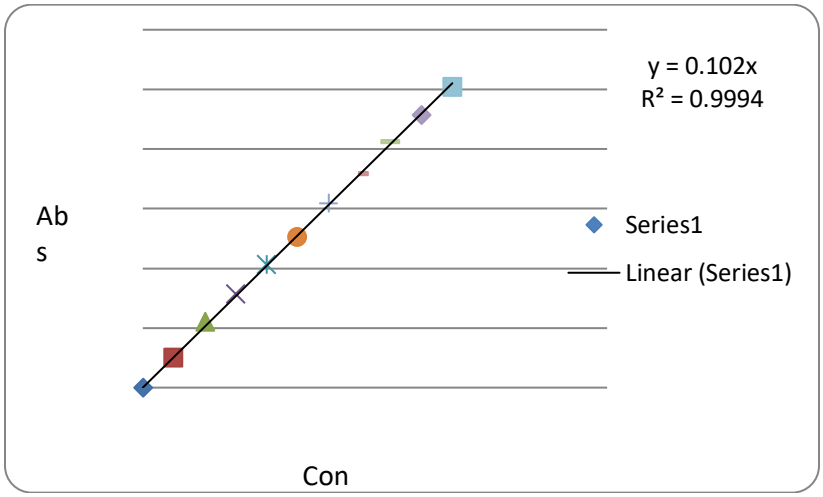
Fourier transform infrared spectra(FTIR)
FTIR spectra for Metoprolol succinate, HPMCK15M and optimized formulations were recorded using a fourier transform infrared spectrophotometer (Perkin Elmer BX_1) samples were prepared using KBr(spectroscopic grade) disks by means of hydraulic pellet press at pressure of 7 – 10 tons .The samples were scanned from 4000 to 400cm^{-1}

Results and Discussion

Spectrophotometric Determination of Metoprolol Succinate

An ultraviolet spectro photometric method was used for estimation of metoprolol succinate. The standard concentration was scanned over a range of 400-200 nm , resulted in a peak at 222nm.The 222nm was taken as absorption maxima for metoprolol succinate.The standard graph and whole analysis was performed in phosphate buffer pH 6.8.

Standard graph of Metaprolol Succinate: The standard graph of Metaprolol Succinate in Phosphate buffer pH 6.8 was plotted. The result shows good linearity with a correlation coefficient of 0.9994 in Phosphate buffer pH 6.8.



Standard graph of Metaprolol succinate

Concentration(µg/ml)	Absorbance at 222nm
0	0
1	0.099
2	0.221
3	0.315
4	0.412
5	0.504
6	0.618
7	0.718
8	0.825
9	0.914
10	1.008

Evaluation of Metaprolol Succinate Sustained Release Tablets [21-28]

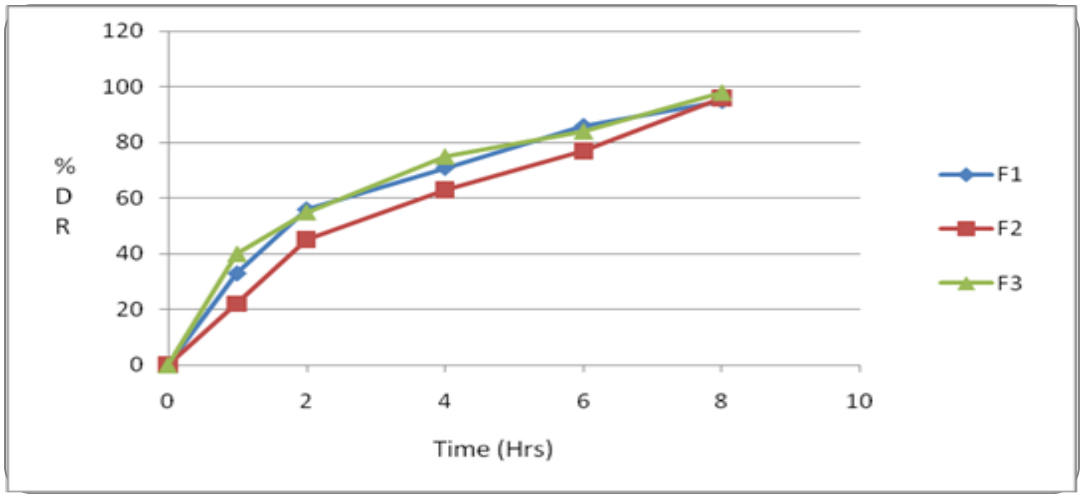
The physical parameters like weight variation, hardness, thickness, drug content of the prepared tablets were within the pharmacopoeial limits. The results of the test were tabulated with the standard deviation

Evaluation of tablets

Formulation	Weight variation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Content Uniformity (mg/tab)
F1	**198±0.7**	**4.4±0.13**	**2.3±0.02**	**0.54±0.01**	**94.69±0.45**
F2	**200±0.5**	**5.4±0.15**	**2.4±0.03**	**0.58±0.02**	**98.76±0.41**
F3	**199±0.6**	**4.6±0.13**	**2.5±0.02**	**0.57±0.01**	**97.99±0.38**
F4	**198±0.8**	**4.3±0.14**	**2.2±0.04**	**0.65±0.03**	**95.80±0.42**
F5	**200±0.7**	**4.8±0.16**	**2.3±0.03**	**0.68±0.01**	**96.79±0.39**
F6	**198±0.6**	**5.0±0.15**	**2.3±0.02**	**0.64±0.03**	**97.90±0.38**
F7	**200±0.5**	**4.5±0.15**	**2.5±0.03**	**0.48±0.02**	**99.45±0.41**
F8	**198±0.6**	**5.0±0.14**	**2.4±0.02**	**0.56±0.01**	**97.67±0.40**
F9	**200±0.7**	**4.4±0.16**	**2.5±0.03**	**0.52±0.03**	**99.08±0.38**

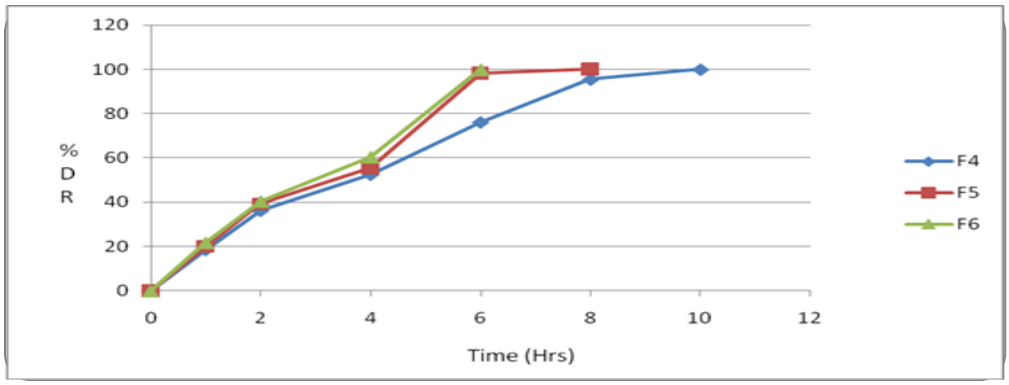
Drug Release Profiles of Metaprolol Succinate Sustained Release Tablets
Cumulative drug release of Formulations F1, F2, F3,

Cumulative % of drug release			
TIME (HRS)	**F 1**	**F 2**	**F 3**
0	0	0	0
1	33	22	40
2	56	45	55
4	71	63	75
6	86	77	84
8	95	96	98



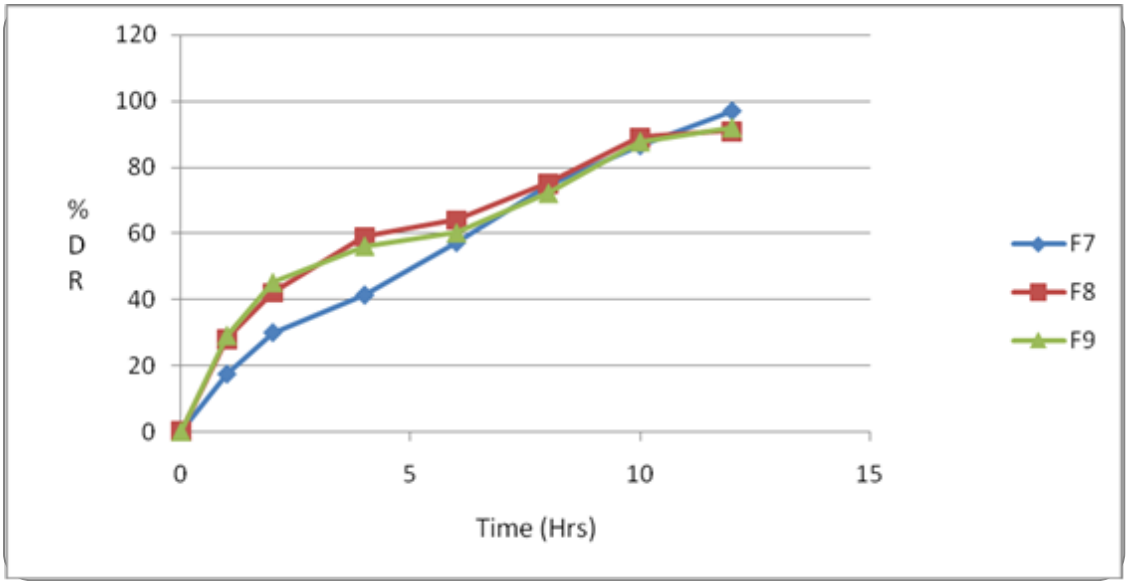
The above figure shows the *in-vitro* release profiles of Metaprolol succinate sustained release tablets of formulations F1, F2, F3. Effect of Ethylcellulose polymer on the release profile of Metaprolol succinate was studied. In formulation F1, F2 and F3 different concentrations of Ethyl cellulose was used. The release of the drug from the tablet was release around95% in 8 hours only, so the polymer is not having the capacity to extend the release up to 12 hours.

Cumulative % of drug release			
TIME (HRS)	**F 4**	**F 5**	**F 6**
0	0	0	0
1	18.51	20.03	21.81
2	36.23	39.24	40.52
4	52.51	55.53	60.49
6	76.15	98.13	100.04
8	95.48	100.10	
10	99.98		



The above figure shows the *In vitro* release profiles of Metaprolol succinate sustained release tablets of formulations F4, F5, F6, effect of HPMC polymer on the release profile of Metaprolol succinate was studied. In formulation F4, F5 & F6 different concentrations of HPMC were used. The release of the drug from the tablet was release up to 10 hours only, So the polymeric not having the capacity to extends the release up to 12 hours.

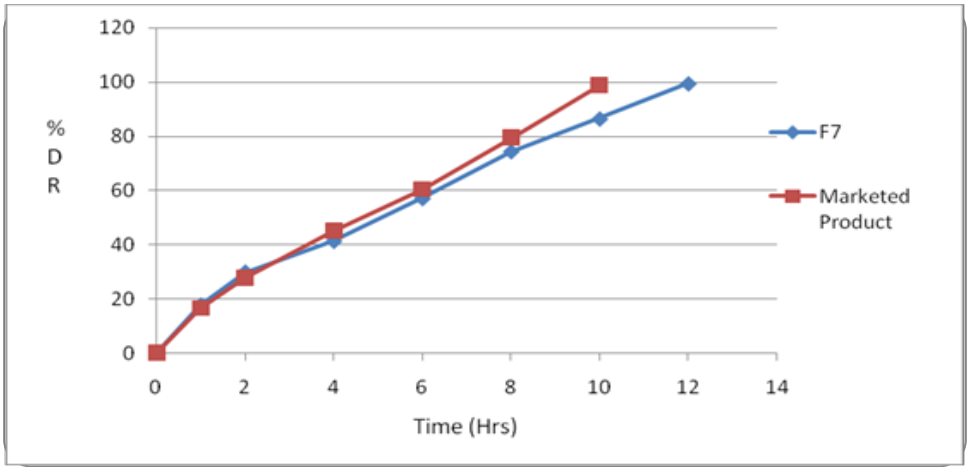
Cumulative % of drug release			
TIME (HRS)	**F 7**	**F 8**	**F 9**
0	0	0	0
1	17.74	28	29
2	29.93	42	45
4	41.3	59	56
6	57.1	64	60
8	74.4	75	72
10	86.5	89	87.6
12	99.5	91	91.8



The above figure shows the *In-vitro* release profiles of Metaprolol succinate sustained release tablets of formulations F7, F8, F9 and the effect of different polymers on the release profile of Metaprolol succinate was studied. In formulation F7, F8 and F9 different concentrations of Ethyl cellulose and HPMC were used. The **F7** formulation tablet was released 99.5% of the drug in12 hours.

Comparisons of in vitro drug release of F7 and Soleken (Marketed porduct)

Time (hrs)	Cumulative % drug release	
	F18	Seloken XL 50mg
0	0	0
1	17.74	16.5
2	29.93	27.8
4	41.3	45.2
6	57.1	60.4
8	74.4	79.5
10	86.5	99.0
12	99.5	

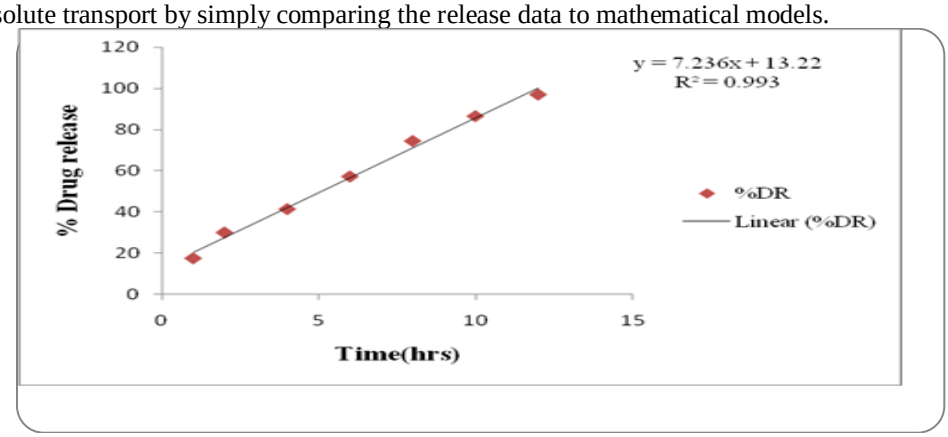


Comparison of % drug release of optimized formulation (F7) and Seloken XL 50mg

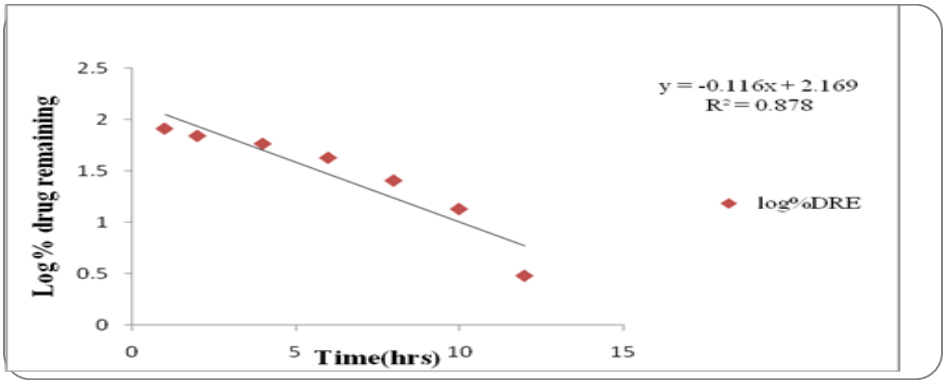
The above figure shows the *In-vitro* release profiles of Metaprolol succinate sustained release tablets of formulations F7, marketed product (Seloken XL) was studied. The release of the drug from the F7 was 99.5% in 12 hrs &marketed product was99% in12hours.

Mathematical Modelling of Foating Tablets [29]

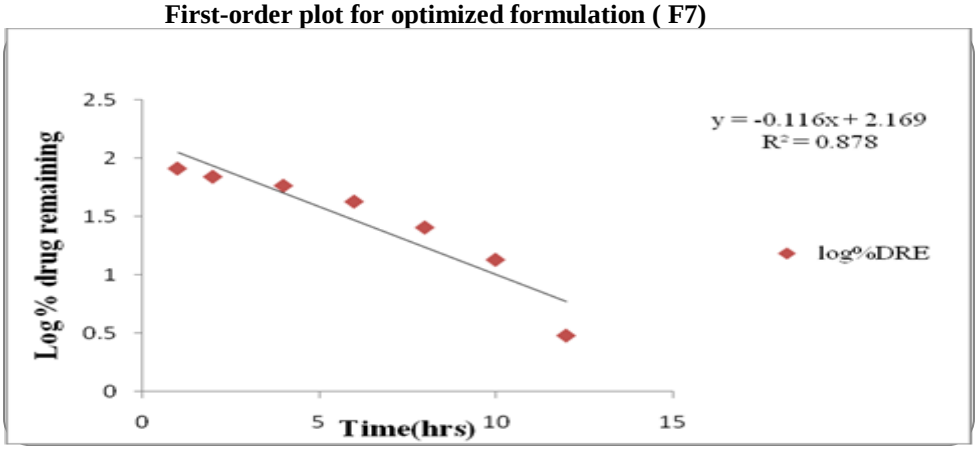
Mathematical modeling of the release kinetics of specific classes of controlled –release systems may be used to predict solute release rates from and solute diffusion behavior through polymers. And elucidate physical mechanisms of solute transport by simply comparing the release data to mathematical models.



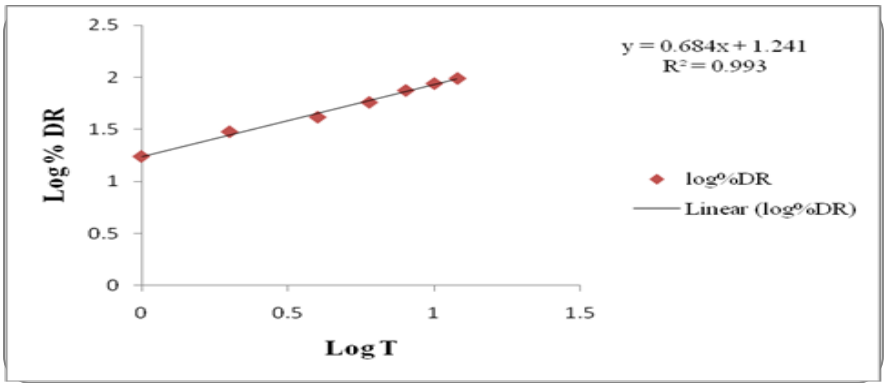
Zero-order plot for optimized formulation (F7)



First-order plot for optimized formulation (F7)



Higuchi plot for optimized formulation (F7)



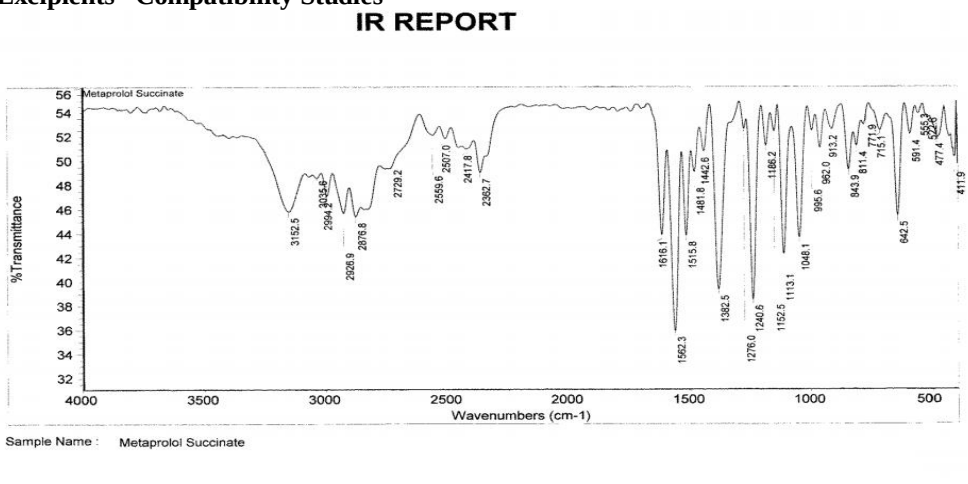
Korsemayer – Peppas plot for optimized formulation (F7)

Release kinetics of optimized formulation (F7)

Formula Code	Zero-order	First – order	Higuchi	Korsemayer-peppas	
	R^2	R^2	R^2	R^2	N
F7	0.993	0.878	0.986	0.993	0.684

From the above results it is apparent that the regression coefficient value closer to unity in case of zero-order plot i.e. 0.993 indicates that the drug release follows a zero- order mechanism and in Korsemayer peppas plot i.e. 0.993 and further the n value obtained from peppas plot i.e. 0.684 suggest that the drug release from tablet was anomalous non fickian diffusion. The mass transfer with respect to square root of time was plotted, revealed a linear relationship with regression value close to one i.e. 0.986 stating that the release from matrix was through diffusion.

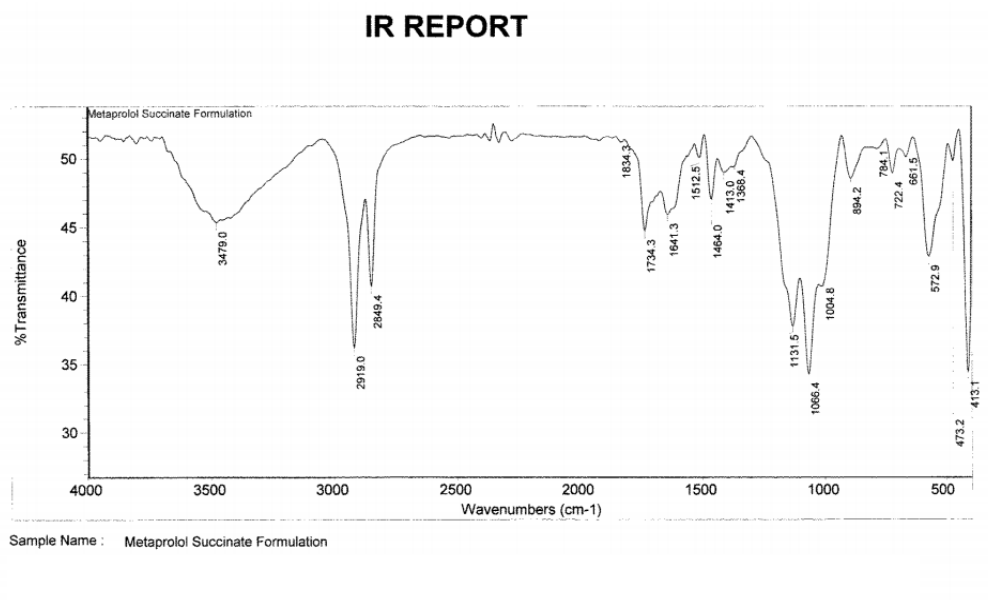
Drug – Excipients Compatibility Studies [30-31]



FTIR spectrum of Metoprolol succinate pure drug

Interpretation of FTIR Results Metoprolol Succinate

FTIR region cm^{-1}	Assignment
1515.8,1616.1	C=C Aromatic stretching
3152.5	C-H Aromatic stretching
2926.9	C-H Aliphatic stretching
1382.5	C-H Aliphatic bending
1240.8	C-O Aromatic stretching
12186.2	C-O Aliphatic stretching



FTIR spectrum of Optimized Formulation (F7)

Interpretation of FTIR Results of optimized formulation (F7)

FTIR region cm^{-1}	Assignment
1512.5,1617.8	C=C Aromatic stretching
3479	O-H stretching
2919.9	C-H Aliphatic stretching
1368.4	C-H Aliphatic bending
1131.6	C-O Aliphatic stretching

In order to get evidence on the possible interactions of drug excipients .FTIR analysis was used. The FTIR spectra of optimized formulation displayed the characteristics peak of drug. Overall there was no alteration in peaks of Metoprolol succinate suggesting that there was no interaction between drug and exipients

Summary

The physical parameters like weight variation, hardness, thickness, drug content of the prepared tablets were within the pharmacopoeial limits.

The in-vitro release profiles of Metaprolol succinate sustained release tablets of formulations F1, F2, F3. Effect of Ethylcellulose polymer on the release profile of Metaprolol succinate was studied.

In formulation F1, F2 and F3 different concentrations of Ethyl cellulose was used. The release of the drug from the tablet was release around 95% in 8 hours only, so the polymer is not having the capacity to extend the release up to 12 hours.

In vitro release profiles of Metaprolol succinate sustained release tablets of formulations F4, F5, F6, effect of HPMC polymer on the release profile of Metaprolol succinate was studied. In formulation F4, F5 & F6 different concentrations of HPMC were used. The release of the drug from the tablet was release up to 10 hours only, So the polymer is not having the capacity to extends the release up to 12 hours.

The *In-vitro* release profiles of Metaprolol succinate sustained release tablets of formulations F7, F8, F9 and the effect of different polymers on the release profile of Metaprolol succinate was studied. In formulation F7, F8 and F9 different concentrations of Ethyl cellulose and HPMC were used. The **F7** formulation tablet was released 99.5% of the drug in 12 hours.

The drug release kinetics shows that, apparent that the regression coefficient value closer to unity in case of zero-order plot i.e. 0.993 indicates that the drug release follows a zero- order mechanism and in Korsemayer peppas plot i.e. 0.993 and further the n value obtained from peppas plot i.e. 0.684 suggest that the drug release from tablet was anomalous non fickian diffusion. The mass transfer with respect to square root of time was plotted, revealed a linear relationship with regression value close to one i.e. 0.986 stating that the release from matrix was through diffusion.

CONCLUSION:

The Sustained release Metaprolol succinate matrix tablets were prepared by direct compression method. The nature of the polymer influences the physical and release characteristics of the matrix tablet. The hydrophobic polymer, Ethyl Cellulose has retarded the drug release from the tablet and the hydrophilic polymer, HPMC has release the drug completely before targeting time (<12 hrs).While making the combination of both hydrophilic and hydrophobic polymers i.e HPMC and Ehyl Eellulose with optimized ratio (F7) leads to sustained release of drug from matrix tablet for 12 hours was observed.

REFERENCES:

1. A. K. Srivastava, Saurabh wadhwa, B.mishra, “oral sustained delivery of Atenolol from floating matrix tablets - formulation and in vitro evaluation.” Drug development and industrial pharmacy, 2005, 31, (4-5), pg 367-374.

2. Ansel HC, Popovich NG, Allen LV. Pharmaceutical dosage forms and drug deliverysystem.B.I. Waverly Pvt. Ltd, New Delhi. 1995; 6:99-154.

3.Atyabi F, Sharma HL, Mohammad HAH, Fell JT. In-vivo evaluation of a novel gastro retentive formulation based on ion exchange resins. J. Control. Rel.1996; 42: 105-13.& Singh BN, Kim HK. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Rel.2000; 63: 235-59.

4. Ayhan Savaşer, Yalçın Özkan· and Aşkın Işımer, **“**Preparation and in vitro evaluation of sustained release tablet formulations of diclofenac sodium” Department of Pharmaceutical Technology, Gülhane Military Medical Academy, Etlik, 06018 Ankara, Turkey. October-2008.

5.Banker GS, Anderson NR; Tablets: Lachman L, Lieberman HA, Kanig JL; The Theory and Practice of Industrial Pharmacy. 3rdedi,Varghese Publication House, Bombay, 1987;296-303.

6.Banker, G.S, and Rhodes C.T., 1996, "Modern Pharmaceutics", 3rd ed., Marcel Dekker, New York pp. 678-721
7.Bexis s, phillis B.D, Ong j , White J.M, Irvine R. J(2004-09)." Baclofen prevents MDMA-inducedrise in core body temperature in rats"74(1):89-96.
8.Blume,R.W.,Davis,R.D., and Keyser, D. J.,2002, "Guaifenesin sustained release formulation and tablets", U.S. Patent No. 6,372,252
9.Bodmeier R, Paeratakul O. The effect of curing on drug release and morphological properties of ethylcellulose pseudolatex-coated beads. *Drug Dev Ind Pharm*1994; **20**(9):
10.Chatap.V.K, Sharma.D.K, Middha.A, Gupta.R.D, Saini.V, Shiradkar.M, Mouth disintegrating tablets of taste masked ondansetron Hcl. Asian J. chem. 2007, 19, 3455-3609
11.D.M.Brahmankar and Sunil B.Jaiswal,Biopharmaceutics and Pharmacokinetics A Treatise",Pg.335-350.
12. D.M. Morkhade, S.V. Fulzele, "Gum Copal and Gum Damar: Novel Matrix forming Materials for Sustained Drug delivery", International Journal of pharmaceutical sciences.2006, pg 53-58.
13.Dressman JB, Derbin GM, Ismailos G, *et al*. Circumvention of pH-dependent release from ethyl cellulose-coated pellets. *J control release* 1995; **36**(3): 251–260.
14. Giovanna Corti, Marzia Cirri, Francesca Maestrelli, Natascia Mennini, "Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-β-cyclodextrin"Europian Journal of pharmaceutics and biopharmaceutics 2008, 68, (2), pg 303-309.
15.GohalM.C, Bansal.G, Bhatt.N, Formulation and evaluation of orodispersible taste masked tablets of Famotidine. Pharma Boil world, 2005, 3, 75-80.
16.Harwood, R.J., 2003, "Hypermelose" in Handbook of pharmaceutical excipients, 4th ed., Raymond C. R., Paul, J. S. and Paul, J.W., Pharmaceutical Press, American Pharmaceutical association, London, U.K. pp. 297-300.
17.Hilton, A. K, and Deasy, P. B., 1992, "In vitro and in vivo evaluation of an oral sustained release floating dosage form of Amoxycyllin trihydrate", Int. J. Pharm., 86, pp. 79-88.
18. hydroxy propyl celluloce – Wikipedia
19. Indian Pharmacopeia Commision
20. John W. Skoug, Martin V. Mikelsons, Cynthia N. Vigneronand Nick L. Stemm "Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms.
21.Kulkarni, A.S. and Bhatia, M.S.,2008, "Design of floating bilayer tablets of diltiazem hydrochloride and lovastatin"PDA J. Pharm. Sci. Technol., 62(5):pp. 344-52.by measurement of polymer release" Control Development, April-1993.
22.Lachman L, Liberman HA and KanigJL. The Theory and Practice of industrial Pharmacy, 3rd Edn, Varghese Publishing House, Bombay 1987: 297-300.
23. Lamotrigine – Rx List..
24.Liandong, H., Li, L., Xun, Y., Wei, L., Jianxue, Y., Yanhong, J.and Chuang, S. H. X.,2011, "Floating matrix dosage form for dextromethorphan hydrobromide based on gas forming technique: In vitro and in vivo evaluation in healthy volunteers" Eur. J.Pharm. Sci.,42(1-2):pp. 99-105.
25.Lisa Brannan-Peppas,Polymers in Controlled Drug Delivary"nov.1997.
26.Milo Gibaldi and Donald Perzier vol.15, Pharmacokinetics" 2nd edn,"revised and expanded Pg.185
27. Mohammad Reza Siahi, Mohammad Barzegar-Jalali, Farnaz Monajjemzadeh, "Design and Evaluation of 1- and 3-Layer Matrices of Verapamil Hydrochloride for Sustaining Its Release". AAPS PharmSciTech. 2005; 6(4): E626-E632.
28.Moursy, N. M., Afifi, N. N., Ghorap, D. M. and El-saharty, J., 2003, "Formulation and evaluation of sustained release floating capsules of Nicardipine hydrochloride' Pharmazie, 58:pp.38-43.
29. Narisawa S, Yoshino H, Hirakawa Y, Noda K. Porosity-controlled ethyl cellulose film coating. IV. Evaluation of mechanical strength of porous ethyl cellulose film. *Chem Pharm Bull* 1994; **42**(7): 1491–1495.
30.Neal M.Davies, "sustained release and enteric coated NSAIDS: Are they really GI safe?", J pharm pharmaceut sci, 1999, 2, (1), pg 5-14.
31. Niazi, Sarfaraz (2004). Handbook of Pharmaceutical Manufacturing Formulations. pp. 275-276. ISBN 0849317460, 9780849317460.