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Review Article

PREFORMULATION STUDIES OF CONTROLLED/SUSTAINED RELEASE FORMULATIONS: AN OVERVIEW

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ABSTRACT
Recently, controlled release drug delivery has become the standards in the modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral Extended release drug delivery medication will continue to account for the largest share of drug delivery systems. The extended release formulations are the type of formulations which will improves the therapeutic index of drug concentration. These formulations make the drug available over extended time period after oral/Parenteral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. Prior to the development of these major dosage forms, it is essential that pertain fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. This information decides many of the subsequent events and approaches in formulation development.
Key words: Sustained/controlled release formulation, Preformulation, Solubility, Partition Coefficient

INTRODUCTION

Sustained release, sustained action, controlled release, extended action, timed release, depot and repository dosage forms are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after the administration of single dose. In the case of injectable drugs this period may vary from days to months. In the case of orally administered forms, this period is measured in hours and is critically depends on the residence time of the dosage form in the GIT. The term "controlled release" has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. The rate controlled drug delivery systems are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and /or targeting the delivery of drug to a tissue. Although these advancements have led to the development of several novel drug delivery systems that could revolutionalize the method of medication and provide a number of therapeutic benefits, they also create some confusion in terminology between 'controlled release' and 'sustained release'[1].

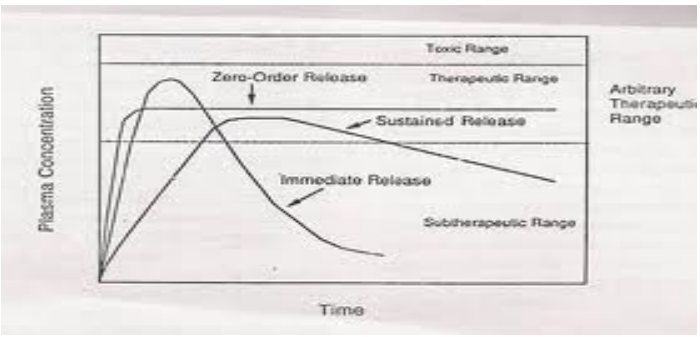


Figure:1

The term "sustained release" has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration (i.e. not necessarily at a predetermined rate). The onset of the pharmacologic action is often delayed, and the duration of its therapeutic agent is sustained.

The term "controlled release" on the other hand, has a meaning that goes beyond the scope of sustained drug action. It also implies a predictability in the drug release kinetics, which means that the release of drug ingredient from a controlled-release drug delivery system proceeds at a rate profile that is not only predictable kinetically but also reproducible from one unit to another[2].

The Concept of Preformulation

Almost all drugs are marketed as tablets, capsules or both. Prior to the development of these major dosage forms, it is essential that pertain fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. This information decides many of the subsequent events and approaches in formation development. This first learning phase is known as pre-formulation. It can be defined as an investigation of physical and chemical properties of new drug substance alone or in combination with other excipient. Pre-formulation is also phase of research & development process where research scientist characterize physical, chemical and mechanical aspect of new drug under investigation in order to developed stable safe & effective dosage form Pre-formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Before beginning the formal pre-formulation programs the pre-formulation scientist must consider the following factors:

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

Pre-formulation drug characterization in a structured program

UV Spectroscopy

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

E = AF / X

Where, A = Asborbance

F = dilution factor

X = weight of drug (mg)

It is now possible to determine concentration of drug in any solution by measuring absorbance[3].

C = AF / E mg/ ml

Characterization of drug molecules is very important step at the pre-formulation phase of product development. Following studies are conducted as basic pre-formulation studies, special studies are conducted depending on the type of dosage form and the type of drug molecules.

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

Solubility Determination

The solubility of drug is an important physicochemical property because it effects the bioavailability of the drug, the rate of drug resale into dissolution medium and consequently, the therapeutic efficiency of the pharmaceutical product. The solubility of the molecules in various solvents is determined as a first step. This information is valuable is developing a formulation. Solubility is usually determined in variety of commonly used solvents and some oils if the molecule is lipophillic. The solubility of material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged until equilibrium achieved[6]

Common solvents used for solubility determination are

Water, Polyethylene Glycols, Propylene Glycol, Glycerin, Sorbitol, Ethyl Alcohol, Methanol, Benzyl Alcohol, Isopropyl Alcohol, Tweens, Polysorbates, Castor Oil, Peanut Oil, Sesame Oil, Buffer at various pHs[6].

Aqueous Solubility

The availability of a drag is always limited and the preformulation scientist may only have 50 mg. Solubility dictates the ease with which formulation for oral gavages and intravenous injection studies in animals are obtained the pKa allies the informed of pH to maintain solubility and to choose salts required to achieve good bioavailability from the solid state and improve stability and powder properties[7].

Intensic Solubility (Co)

An increase in solubility in acid compared to aqueous solubility suggests a weak base and an increase in alkali, a weak acid. An increase in acidic and alkaline solubility suggest either impotence or zuitter ion behavior. In this case there will be two pKa's, one acidic & one basic. When the pavrity of the drug sample can be assured the solubility obtained in acid for a weak acid or albali for a weak base can be assured to be the instensic solubility (Co.) i.e. the fundamental solubility when completely unionized. The solubility should ideally be measured at two temperature.

1) 4C to ensure physical stability and entered short term storage and chemical stability unit more definitive data are available. The minimum density of water occurs at 4C. This leads to a minimum aqueous solubility.

2) 37 ^{o}C to support biopharmaceutical evaluation.

pKa Determination

Determination of the dissociation content for a drug capable of ionization within a ph rang of 1 to 10 is important since solubility and consequently absorption, cab be altered by orders of magnitude with changing pH. The Henderson – Hasseslebach equation provides an estimate of the ionized and un ionized durg concentration at a particular pH.

For acidic compounds

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

Partition Coefficient

Partition Coefficient (oil/ water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes. It is defined as the ratio of unionized drug distributed between the organic and aqueous phases at equilibrium.

P o/w = (C oil / C water) equilibrium.

For series of compounds, the partition coefficient can provide an empiric handle in screening for some biologic properties. For drug delivery, the lipophilic/ hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption. Although partition coefficient data alone does not provide understanding of in vivo absorption, it does provide a means of characterizing the lipophilic/ hydrophilic nature of the drug. Since biological membranes are lipoidal in nature. The rate of drug transfer for passively absorbed drugs is directly related to the lipophilicity of the molecule. The partition coefficient is commonly determined using an oil phase of octanol or chloroform and water. Drugs having values if P much greater than 1 are classified as lipophilic, whereas those with partition coefficient much less than 1 are indicative of a hydrophilic drug. Although it appears that the partition coefficient may be the best predictor of absorption rate, the effect id dissolution rate, pKa and solubility on absorption must not be neglected[8]

Dissolution

The dissolution rate of the a drug is only important where it is the rate limiting step in the absorption process. Kaplan suggested that provided the solubility of a drug exceeded to mg/ ml at pH, 7 no bioavailability or distinction related problems were to be expected. Below / mg/ ml such problems were quite possible and salt formation could improve absorption and solubility by controlling the pH of the microenvironment, independently of the drug and dosage forms position within the GI Tract[10].

Intrinsic Dissolution Rate

When dissolution is controlled solely by diffusion the rate of diffusion is directly proportional to the saturated concentration of the drug in solution under these conditions the rate constant K_1 is defined by

$K_1 = 0.62\ D^{2/3}\ v^{1/6}\ w^{1/2}$

Where, V is the kinemative viscosity

W is the anguter velocity of a rotating disc of drug.

Common Ion Effect

A common ion significantly reduces, the solubility of a slightly soluble electrolyte. The 'selling out' results from the removal of water molecules as solvent owing to the completing hydration of other ions. The reverse process

'salting in' qries with large anions e.g. benzoate, salivate which open the water structure. These hydro topics increase the solubility of properly water soluble compounds such as diazepam.

Melting Point

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

1)Capillary Melting

2)Hot Stage Microcopy

3)Differential scanning calorinetry or thermal Analysis.

Capillary Melting

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

Hot Stage Microcopy

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

Differential Scanning Calorimeltry and thermal analysis

Differential thermal analysis (DTA) measures the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant rate differential scanning calorinetry (DSC) is similar to DTA except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference i.e. it measures the enthalpy of transition[11].

Crystal Properties and Polymorphism

Many drug substance can exit in more than one crystalline from with different space lattice arrangements. This property is known as polymorphism. Polymorphs generally have different melting points, x-ray diffraction patterns and solubility even though they are chemically identical. Differences in the dissolution rates and solubilities of different polymorphic forms of a given drug are very commonly observed. When the absorption of a drug is dissolution rate limited, a more soluble and faster-dissolving from may be utilized to improve the rate and extent of bioavailability.For drugs pane to degradation in the solid state, physical form of the drug influences degradation. Selection of a polymorph that is chemically more stable is a solution in many cases. Different polymorph also lead to different morphology, tensile strength and density of power bed which all contribute of compression characteristics of materials. Some investigation of polymorphism and crystal habit of a drug substance as it relates to pharmaceutical processing is desirable during its Preformulation evaluation especially when the active ingredient is expected to constitute the bulk of the tablet mass. Although a drug substance may exist in two or more polymorphic forms, only one form is theromdynamically stable at a given temperature and pressure. The other forms would convert to the stable form with time. In general, the stable polymorph exhibits the highest melting point , the lowest solubility, and the maximum chemical stability. Various techniques are available for the investigation of the solid state. These include microscopy (including hot stage microcopy), infrared spectrophotometry, single-crystal x-ray and x-ray power diffraction, thermal analysis, and dilalometry.

Particle Size, Shape and Surface Area

Bulk flow, formulation homogeneity, and surface-area controlled processes such as dissolution and Surface morphology of the drug particles. In general, each new drug candidate should be tested during Preformulation with the smallest particle size as is practical to facilitate preparation of homogeneous samples and maximize the drug' s surface area for interactions. Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also, in some instances, on their biopharmaceutical behavior. It is generally recognized that poorly soluble drugs showing a dissolution- rate limiting step in the absorption process will be more readily bio available when administered in a finely subdivided state rather than as a coarse material. In case of tablets, size and shape influence the flow and the mixing efficiency of powders and granules. Size can also be a factor in stability: fine materials are relatively more open to attack from atmospheric oxygen, the humidity, and interacting axcipients than are coarse materials[12].

- Determination of particle size
- Determination of surface area

Particle size Determination

Though microscopy is the simplest technique of estimating size ranges and shapes, it is to slow for quantitative determination the material is best observed as a suspension in non dissolving fluid. Saving is less useful technique at pre-formulation storage due to lack of bulk material. Andreason pipette is based on the rate difference of sedimentation of different particles, but techniques like this are seldom used due to their tedious nature instruments based on light scattering, (Royco), light blockage (HIAC) and blockage of electrical conductivity path (coulter counter) are available.

Surface Area Determination

Surface area is most commonly determined based on brunaver emette teller (BET) theory of adsorption. Most substances adsorb a mono molecular layer of gas under certain conditions of partial pressure of gas and temperature. Knowing the monolayer capacity of adsorbent and the area of absorbale molecule, the surface area can be calculated the adsorption process is carried out with nitrogen at-195 degree Celsius at a partial pressure attainable when nitrogen is in a 30% temperature with an inert gas (helium). The adsorption takes place by virtue of vander wall's forces.

Power Flow Properties

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

Bulk Density

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

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Pored density} * 100}{\text{Tapped density}}$$

A similar index has been defined by Hausner:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Pored density}}$$

Angle of repose

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

Chemical stability profile

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a new drug. These studies include both solution and solid state

experiments under condition typical for the handing, formulation, storage, and administration of a drug candidate as well as stability in presence of other recipients.

Factor effecting chemical stability critical in rational dosage form design include temperature, pH and dosage form diluents. The method of sterilization of potential product will be largely dependent on the temperature stability of the drug. Drugs having decreased stability at elevated temperatures cannot be sterilized by autoclaving but must be sterilized by another means, e.g., filtration. The effect of pH on drug stability is important in the development of both oral administration must be protected from the highly acidic environment of the stomach. Buffer selection for potential dosage forms will be largely based on the stability characteristic of the drug.

- Solid state stability Solution phase stability
- Compatibility studies : stability in the Presence of excipients
- Typical stability protocol for new Chemical Entity

Solid state stability

Chemical instability normally results from either of the following reaction :- hydrolysis, oxidation, photolysis and pyrolysis, Chemical structure of the drug is the determination of drug to either of these attacks. Esters and lactase and to lesser extent, amides are to prone to solvolysis Instauration or electron rich centre in the structure make the molecule vulnerable for free radical mediated or photo-catalysed oxidation. physical properties of drugs. Amorphous materials are less stable than their crystalline forms. Denser materials are more stable to ambient stress.

Elevated temperature studies

The elevated temperatures commonly used are 40, 50, and 60 degree centigrade with ambient humidity. The samples stored at highest temperature are observed weekly for physical and chemical changes and compared to an appropriate control. If a substantial change is seen, samples stored at lower temperature are examined. If no changesisseen after 30 days at 60 degree centigrade, the stability prognosis is excellent.

Stability under high humidity conditions

Solid drug samples can be exposed to different relative humidity conditions by keeping them in laboratory desiccators containing saturated solutions of various salts. The closed desiccators in turn are kept in oven to provide constant temperature. The preformulation data of this nature are useful in determining if the material should be protected and stored in controlled low humidity environment or if non aqueous solvent be used during formulation.

Photolytic stability

Many drugs fade or dorpen on exposure light. Though the extent of degradations small and limited to the exposed surface area, it presents anaesthetic problem. Exposure of drug 400 and 900 foot-candles of illumination for 4 and 2 week periods respectively is adequate to provide some idea of photosensitivity. Resulting data may be useful in determining if an amber colored container is required or if color masking bye should be used in the formulation.

Stability to Oxidation

Drug's sensitivity to oxidation can be examined by exposing it to atmosphere of high oxygen tension. Usually a 40% oxygen atmosphere allows for rapid evaluation. A shallow layer of drug exposed to a sufficient headspace volume ensures that the system is not oxygen limited. Samples are kept in desiccators equipped with three-way stop cocks, which are alternatively evacuated and flooded with desired atmosphere. The process is repeated 3 or 4 times to ensure 100% desired atmosphere. Results may be useful in predicting if an antioxidant is required in the formulation or if the final product should be packaged under inert atmospheric conditions.

Compatibility studies

The knowledge of drug excipients interaction is useful for the formulation to select appropriate excipients. The described preformulation screening of drug excipients interaction requires only 5mg of drug in a 50% mixture with the excipients to maximize the likelihood of obscuring an interaction. Mixtures should be examined under nitrogen to ultimate oxidation and paralytic effect at a standard heating rate on DSC, over a temperature range, which will encompass any thermal changes due to both the drug and appearance or disappearance one or more peaks in themogrames of drug excipient mixtures are considered of indication of interaction.

Solution phase stability

As compared with the dry form, the degradation is much rapid in solution form. It is important ascertain that the drug doesn't degrade when exposed to GI fluid. The pH based stability study, using different stimulator GI condition can be designed. A poor solution stability of drug may urge the formulator to choose a less soluble salt form, provided the bioavailability is not compromised

Absorption behavior

It is essential to test the in vivo behavior of the new drug for successful formulation of a dosage from good bioavailability. Partial in vivo and in vitro test are designed to study pharmacokinetic profile of the drug.

Factors affecting Controlled Release Dosage Forms

Dose Size

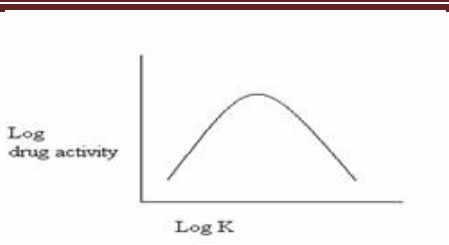
If an oral product has a dose size greater that 0.5gm it is a poor candidate for sustained release system, Since addition of sustaining dose and possibly the sustaining mechanism will, in most cases generates a substantial volume product that unacceptably large.

Aqueous Solubility

Most of drugs are weak acids or bases, since the unchanged form of a drug preferentially permeates across lipid membranes drugs aqueous solubility will generally be decreased by conversion to an unchanged form for drugs with low water solubility will be difficult to incorporate into sustained release mechanism. The lower limit on solubility for such product has been reported 0.1mg/ml. drugs with great water solubility are equally difficult to incorporate in to sustained release system. pH dependent solubility, particularly in the physiological pH range, would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate**.**

Partition Coefficient

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly compounds with relatively high partition coefficient are predominantly lipid soluble and consequently have very low aqueous solubility. Compounds with very low partition coefficients will have difficulty in penetrating membranes resulting poor bioavailability. Typical relationship between drug activity and partition Coefficient K, generally known as Hansh Correlation.



Pka: It is the relationship between Pka of compound and absorptive environment. Presenting drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form

Drug Stability

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. Degradation will proceed at the reduced rate for drugs in the solid state, for drugs that are unstable in stomach, systems that prolong delivery ever the entire course of transit in GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered form a sustaining dosage from. This is because more drug is delivered in small intestine and hence subject to degradation

Molecular size and diffusivity

The ability of drug to diffuse through membranes its so called diffusivity & diffusion coefficient is function of molecular size (or molecular weight).Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 to 10-9 cm2 / sec. with values on the order of 10-8 being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 cm2/sec. Thus high molecular weight drugs and / or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

Biological Half Life

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To action this, drug must enter in the circulation of approximately the same rate of which it is eliminated. The elimination rate is quantitatively described by half-life ($t_{1/2}$). Therapeutic compounds with short half lives are excellent candidates for sustained release preparations. Since this can reduce dosing frequency. In general drugs with half-lives shorter than 3hrs are poor candidates of sustained release dosage forms of dose size will increase as well as compounds with long half lives, more than 8 hrs are also not used in sustained release forms because their effect is already sustained.

Absorption

The rate, extent and uniformity of absorption of a drug are important factors when considered its formulation into a sustained release system. As the rate limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption. Rapid rate of absorption of drug, relative to its release is essential if the system is to be successful. It we assume that transit time of drug must in the absorptive areas of the GI tract is about 8-12 hrs. The maximum half life for absorption should be approximately 3-4 hrs. Otherwise device will pass out of potential absorption regions before drug release is complete.

Distribution

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/ controlled release products, one must have information of disposition of drug.

CONCLUSION

Preformulation studies have a significant part to play in anticipating formulation problems and identifying logical path in both liquid and solid dosage form technology. The need for adequate drug solubility can not be overemphasized. The most appropriate salt for development. Stability studies in solution will indicate the feasibility of parental or other liquid dosage form and can identify methods of stabilization. In parallel solid-state stability by DSC, TLC and HPLC in the presence of tablet and capsule excipient will indicate the most acceptable vehicles for solid dosage form.

By comparing the physicochemical properties of each drug candidate with in a therapeutic group, the preformulation scientist can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response and advise the bulk chemist about the selection and production of the best salt with appropriate particle size and morphology for subsequent processing.

REFERENCES

1. Kandavilli S, Nair V, Panchagnula R. Polymers in transdermal drug delivery systems, Pharmaceutical Technology 2002, 62-78.
2. Guy RH. Current status and future prospects of transdermal drug delivery, Pharm Res 1996, 13, 1765-1769.
3. Guy RH, Hadgraft J, Bucks DA. Transdermal drug delivery and cutaneous metabolism, Xenobiotica 1987, 7, 325-343.
4. Chein YW. Transdermal Controlled Systemic Medication. New York and Basel, Marcel Dekker Inc. 1987; 159 – 176.
5. Keith AD. Polymer matrix considerations for transdermal devices, Drug Dev. Ind. Pharm 1983, 9, 605.
6. Baker RW, Heller J. Material selection for transdermal delivery systems; In: Hadgraft J, Guys RH, editors. Transdermal Drug Delivery: Development Issues and Research Initiatives. New York, Marcel Dekker Inc. 1989; 293-311.
7. Guyot M, Fawaz F. Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol, Int J Pharm 2000, 204, 171-182.
8. Gabiga H, Cal K, Janicki S. Effect of penetration enhancers on isosorbide dinitrate penetration through rat skin from a transdermal therapeutic system, Int J Pharm 2000, 199, 1-6.
9. Minghetti P, Cilurzo F, Casiragh A, Molla FA, Montanari L. Dermal patches for controlled release of miconazole: Influence of drug concentration on the technical characteristics, Drug Dev Ind Pharm 1999, 25, 679-684.
10. Tsai CJ, Hu LR, Fang JY, Lin HH. Chitosan hydrogel as a base for transdermal delivery of berberine and its evaluation in rat skin, Biol. Pharm. Bull 1999, 22, 397-401.
11. Bromberg L. Cross linked polyethylene glycol networks as reservoirs for protein delivery, J Apply Poly Sci 1996, 59, 459-466.
12. Verma PRP, Iyer SS. Transdermal delivery of propranolol using mixed grades of eudragit: Design and in vitro and in vivo evaluation, Drug Dev Ind Pharm 2000, 26, 471-476.
13. Ubaidulla U, Reddy MV, Ruckmani K, Ahmad FJ, Khar RK. Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on *in vitro* and *in vivo* characteristics, AAPS PharmSciTech 2007, 8(1)
14. Gannu R, Vamshi Vishnu Y, Kishan V, Madhusudan Rao Y. Development of nitrendipine transdermal patches: In vitro and ex vivo characterization, Current Drug Delivery 2007, 4, 69-76.
15. Gale R, Spitze LA. Permeability of camphor in ethylene vinyl acetate copolymers. In proceedings: Eighth International Symposium on Controlled Release of Bioactive Materials. Minneapolis, MN, Controlled Release Society. 1981; 183.