DESIGN AND EVALUATION OF CONTROLLED RELEASE FORMULATIONS OF IBUPROFEN TABLET

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In partial fulfillment of the requirement for the award of degree of

MASTER OF PHARMACY

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by

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UNDER THE GUIDANCE OF

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MARCH 2011.

CERTIFICATE

This is to certify that the dissertation entitled **"DESIGN AND EVALUATION OF CONTROLLED RELEASE FORMULATIONS OF IBUPROFEN TABLET"** is a bonafide and genuine research work carried out by **Mr. VIKRAM KUDUMULA** during the year 2010-2011 under the supervision of **Miss. P.KAVITHA, M.Pharm., Asst. Professor**, Department of Pharmaceutics**,** K.K College of Pharmacy, Chennai – 600122. This is the dissertation submitted in partial fulfillment for the award of degree of Master of Pharmacy (Pharmaceutics) by The Tamilnadu Dr.M.G.R. Medical University, Chennai-32

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VIKRAM KUDUMULA

Dedicated to my Parents

&

Almighty

ABBREVATIONS

%RH	- Percentage Relative humidity
BD	- Bulk Density
CI	- Carr's Index
cm	- Centimeters
gm	- Gram
HR	- Hausner's Ratio
Kp	- Kilo Pounds
ml	- Milliliters
mm	- Millimeters
^{o}C	- Centigrade
RPM	- Revolutions Per minute
TD	- Tapped Density

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1. INTRODUCTION

1.1 CONTROLLED DRUG DELIVERY SYSTEM[1].

Therapeutic efficacy and safety of drugs, administrated by conventional methods, can be improved by more precise spatial and temporal placement within the body, thereby reducing both the size and number of doses by using controlled drug delivery system. An ideal controlled drug delivery system is the one which delivers the drug at predetermined rate, locally or systemically for a specified period of time. An ideal targeted drug delivery system delivers the drug only to its site of action.

An ideal drug delivery system should deliver the drug at a rate dictated by the needs of the body over the period of treatment channel the active entity solely to the site of action. To make it in practice various controlled and targeted drug delivery system are introduced. Controlled delivery of drugs, proteins and other bioactive agents can be achieved by incorporating them either in dissolved or dispersed form in polymers.

In general controlled delivery attempts to, Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern. Localize drug action by spatial placement of a controlled release system (rate controlled) adjacent to or in the diseased tissue or organ. Target drug action by using carriers to deliver drugs to particular target cell type.

1.1.1 OBJECTIVES OF CONTROLLED DRUG DELIVERY SYSTEMS.

The chief objective of most products should be controlled delivery to reduce dosing frequency to an extend that once daily does is sufficient for therapeutic management though a uniform plasma concentration at a steady state. The major objectives include,

I. Predict drug release rated form and drug diffusion behaviour through polymers, thus avoiding excessive experimentation.

II. Elucidate the physical mechanism of drug transport by simply comparing the release data mathematical models.

III. Design new drug delivery system based on general release expressions.

IV. Optimize the release kinetics.

1.1.2 FACTOR INFLUENCING THE DESIGN AND PERFORMANCE OF CONTROLLED DRUG DELIVERY SYSTEM[1].

I. Biopharmaceutical characteristic of the drug.

   a. Molecular weight of the drug.

   b. Aqueous solubility of the drug.

   c. Apparent partition coefficient.

   d. Drug pKa and ionization physiological pH.

   e. Drug stability.

   f. Mechanism and site of absorption.

   g. Route of administration.

II. Pharmacokinetic characteristic of the drug.

   a. Absorption rate.

   b. Elimination half life.

   c. Rate of metabolism.

   d. Dosage form index.

III. Pharmacodynamics characteristic of the drug.

   a. Therapeutic range.

   b. Therapeutic index.

   c. Plasma–concentration–response relationship.

1.1.3 CLASSIFICATION OF CONTROLLED DRUG DELIVERY SYSTEMS[1].

1.1.3.1 ORAL CONTROLLED DRUG DELIVERY SYSTEM.

a. Continuous release system.
b. Dissolution controlled release system.
c. Diffusion controlled release system.
d. Diffusion and dissolution controlled release system.
e. Ion exchange resin drug complexes.
f. Slow dissolving salt and complexes.
g. pH independent formulations.
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a. Altered density system.
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1.1.4 ADVANTAGES OF CONTROLLED DRUG DELIVERY SYSTEMS[1,2].

I. Improved patient convenience and compliance due to less frequency of dosing.
II. Reduction in fluctuation in steady-state levels and therefore better control of disease condition and less side effects.
III. Increased safety margin of high potency drug.
IV. Low dose requirement because of maximum utilization of drug.
V. Reduction in health care cost.

1.1.5 DISADVANTAGES OF CONTROLLED DRUG DELIVERY SYSTEMS[1,2].

I. Decreased systemic availability.
II. Poor *in vitro- in vivo* correlations.
III. Chances of dose dumping.
IV. Dose withdrawal is not possible.
V. Higher cost of formulation.

1.2 SUSTAINED RELEASE DOSAGE FORMS[3,4].

A sustained-release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug". The primary objectives of sustained drug delivery are to ensure safety and enhancement of efficacy of drug with improved patient compliance. This delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above the minimum effective concentration and below the minimum toxic level for an extended period of time. Thus, sustained drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects. Simply it can describe the slow release of a drug substance from a dosage form to maintain therapeutic response for extended period (8-12h) of time. Time depends on the dosage form. In oral form it is in hours, and in parenteral's it is in days and

months. Ex: Aspirin SR, Dextrin SR. In case of Controlled release dosage form the rate or speed at which the drug is released is controlled. Ex: Adalat CR (Nifidipine), Dynacirc CR (Isradipine)**.**

The aim of any drug delivery system is to provide therapeutic amount of drug to appropriate site in the body to achieve immediate therapeutic response and to maintain the desired drug concentration. In the recent years sustained release (SR) dosage forms continue to draw attention in the research for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release, sustained action, prolonged action, extended action are the terms used to identify drug delivery system that are designed to achieve a prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose**.**

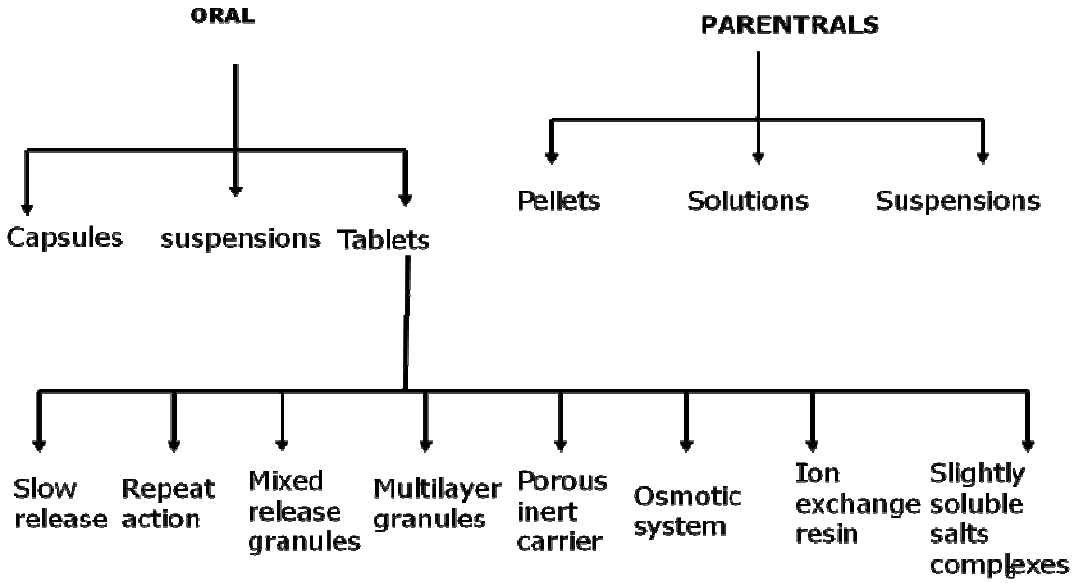

Fig 1. Classification of dosage forms.

1.2.1 Advantages of Sustained release dosage forms[5].

I. Improved patient compliance:
   i. Less frequent dosing
   ii. Allows whole day coverage.

II. Decreased local and systemic side effects.
   i. Decreased GIT irritation.
   ii. Decreased local inflammation.

III. Better drug utilization.
   i. Decreased total amount of drug used.
   ii. Minimum drug accumulation on chronic dosing.

IV. Improved efficiency in treatment.
   i. Uniform blood and plasma concentration.
   ii. Decreased fluctuation in drug level i.e. uniform pharmacological response.
   iii. Increased bioavailability of some drugs.

V. Optimization of duration of action of drug.

VI. Controlling the site release.

VII. Economy.

1.2.2 Disadvantages of Sustained release dosage forms.

I. Increased variability among dosage units.

II. Stability problems.

III. Increased cost per unit dose.

IV. More rapid development of tolerance.

V. Need of additional patient education and counselling**.**

1.2.3 Factors to be considered while formulating a sustained release dosage forms.

I. Drug properties: Stability, solubility, partition coefficient and protein binding are to be considered.

II. Route of drug delivery: Area of the body where drugs are applied or administered plays a vital role.

III. Target sites: To minimize side effects, it's desired to maximize the fraction of dose applied.

IV. Acute or chronic dosing: Cure, Control and length of drug therapy must be considered.

V. The disease: Pathological conditions play a significant role.

VI. The patient: Ambulatory/ bedridden, young or old, etc., must be considered[5].

1.2.4 TECHNIQUES FOR PREPARING SR FORMULATIONS[5].

1.2.4.1 BASED ON DRUG MODIFICATION.

Complex formation - The rate of dissolution of solid complex in biological fluids and rate of dissociation of complex in the solution are considered and they depend upon pH and composition of gastric and intestinal fluids.

Drug-adsorbate preparation - In this product is insoluble. Drug availability is determined by rate of disabsorption.

Pro drug synthesis - They are inactive and need enzymatic hydrolysis for regeneration. Solubility, absorption rate of pro drug must be lower than parent drug.

Ion exchange resins - They are water insoluble, cross linked polymers containing salt forming groups. The drug is bound to the resin by using chromatographic column or by prolonged contact.

Drug release from this complex depends on pH & property of resin. Drug that is attached to the resin is released by exchanging with the ions present in the GIT

$Resin^{+}\text{-}Drug^{-} + X^{-} \dashrightarrow Resin^{+}\text{-}X^{-} + Drug$, Example: Biphetamine.

1.2.4.2 BASED ON DOSAGE FORM MODIFICATION.

Micro encapsulation - It's a process in which tiny particles are surrounded by uniform coating (microcapsule) or held in a matrix of polymer (microsphere.) Spray drying is used which involves rapid evaporation of the solvent from the drug surface.

Barrier coating: In this one quarter of the granules are in non sustained form for sudden drug release, remaining part is coated for sustained release. Both these granules are filled in hard gelatine capsule or compressed in a tablet, and the release mechanism is by diffusion. Coating material used are fats, waxes.

Matrix embedding - Drug is dispersed in a matrix of retardant material which may be encapsulated or compressed in a tablet. Mechanism of Drug Release from Matrix Tablets - As shown in Fig 2, in erodible matrices, polymer erosion from the surface of the matrix determines the drug release; whilst in hydrophilic matrices, formation of the gel layer and its dynamics as a function of time determines the drug release. Gel layer thickness, which determines the diffusion path length of the drug, corresponds to the distance between the diffusion and erosion fronts. As the swelling process proceeds, the gel layer gradually becomes thicker, resulting in progressively slower drug-release rates; however, due to continuous hydration, polymer disentanglement occurs from the surface of the matrix, resulting in a gradually decreasing depletion zone and an increased dissolution rate.Schematic drug release from matrix diffusion controlled-release drug delivery systems with the drug homogenously dispersed in: (a) an erodible polymer matrix; and (b) a hydrophilic, sellable polymer matrix.

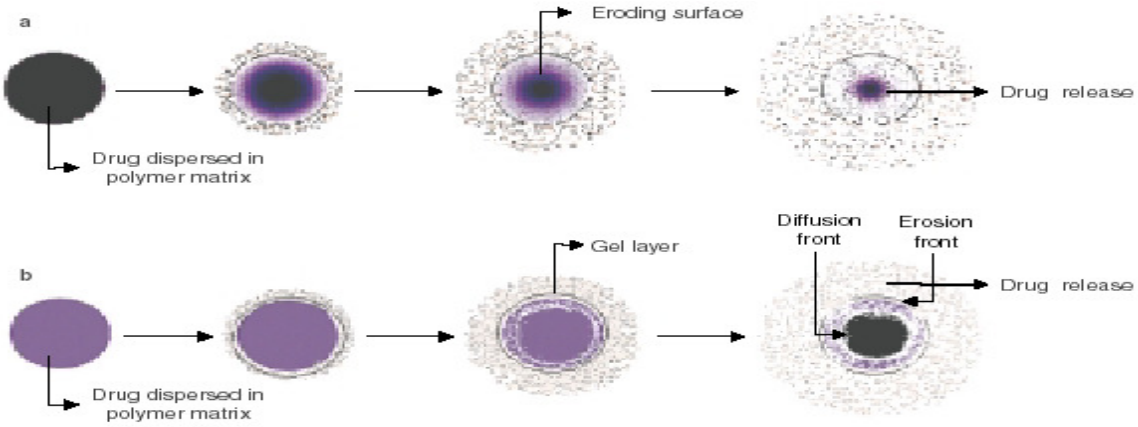

Fig 2. Mechanism of drug release from matrix tablets.

1.3 TABLETS[5].

1.3.1 Introduction[5].

A tablet is a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. The excipient include binders, glidants (Flow aids) and lubricants to ensure efficient tableting disintegrants to ensure that the tablet breaks up in the digestive tract; sweeteners or flavours to mask the taste of bad-tasting active ingredients; and pigments to make uncoated tablets visually attractive. A coating may be applied to hide the taste of the tablet's components, to make the tablet smoother and easier to swallow, and to make it more resistant to the environment, extending its shelf life. Tablets may be swallowed whole or being chewed. Some are dissolved or dispersed in water before administration. Some are put in oral cavity, where the active ingredient is liberated at a predetermined rate. Implants may also be presented in form of tablet**.**

Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance and the intended mode of administration. The compressed tablet is the most popular dosage form in use today. About two-thirds of all are dispensed as solid dosage forms, and half of these are compressed tablets. A tablet can be formulated to deliver an accurate dosage to a specific site; it is usually taken orally, but can be administered sublingually, buccally, rectally or intra vaginally. The tablet is just one of the many forms that an oral drug can take such as syrups, elixirs, suspensions, and emulsions. Medicinal tablets were originally made in the shape of a disk of whatever colour their components determined, but are now made in many shapes and colors to help distinguish different medicines. Tablets are often stamped with symbols, letters, and numbers, which enable them to be identified. Sizes of tablets to be swallowed range from a few millimeters to about a centimetre**.**

1.3.2 VARIOUS TYPES OF TABLETS.

1.3.2.1 ORAL TABLETS FOR INGESTION.

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

I. Standard compressed tablet.
II. Multiple compressed tablet.

   i. Compression coated tablet.
   ii. Layered tablet.
   iii. Inlay tablet.

III. Modified Release tablet.
IV. Delayed action tablet.
V. Targeted tablet.

   i. Floating tablet.
   ii. Colon targeting tablet.

VI. Chewable tablet.
VII. Dispersible tablet.

1.3.2.2 TABLETS USED IN THE ORAL CAVITY.

The tablets under this group are aimed release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

I. Lozenges and troches.

II. Sublingual tablet.

III. Buccal tablet.

IV. Dental cones.

V. Mouth dissolved tablet.

1.3.2.3 TABLETS ADMINISTERED BY OTHER ROUTES.

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

I. Vaginal tablet.

1.3.2.4 TABLETS USED TO PREPARE SOLUTION.

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used.

I. Effervescent tablet

II. Hypodermic tablet

III. Soluble tablet

1.3.3 TABLET PROPERTIES[5].

Tablets can be made in virtually any shape, although requirements of patients and tableting machines mean that most are round, oval or capsule shaped. More unusual shapes have been manufactured but patients find these harder to swallow, and they are more vulnerable to chipping or manufacturing problems. Tablet diameter and shape are determined by the machine tooling used to produce them - a die plus an upper and a lower punch are required. This is called a station of tooling. The thickness is determined by the amount of tablet material and the position of the punches in relation to each other during compression. Once this is done, we can measure the corresponding pressure applied during compression. The shorter the distance between the punches, thickness, the greater the pressure applied during compression and sometimes the harder the tablet. Tablets need to be hard enough that they don't break up in the bottle, yet friable enough that they disintegrate in the gastric tract**.**

Tablets need to be strong enough to resist the stresses of packaging, shipping and handling by the pharmacist and patient. The mechanical strength of tablets is assessed using a combination of (i) simple failure and erosion tests, and (ii) more sophisticated engineering tests. The simpler tests are often used for quality control purposes, whereas the more complex tests are used during the design of the formulation and manufacturing process in the research and development phase. Standards for tablet properties are published in the various international pharmacopeias (USP/NF, EP, JP, etc). Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall. Common minerals like talc or silica, and fats, e.g. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules.

1.3.4 Advantages of tablet as a dosage form.

I. Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.

II. Inaccuracy of dose is maintained since tablet is a solid unit dosage form.

III. Tailor made release profile can be achieved.

IV. Longer expiry period and minimum microbial spillage owing to lower moisture content.

V. As tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.

VI. Ease of packaging (blister or strip) and easy handling over liquid dosage form.

VII. Easy to transport in bulk. Emergency supply supplies can be carried by patients.

VIII. Organoleptic properties (taste, appearance and odour) are best improved by coating of tablet.

IX. Product identification is easy and markings done with the help of grooved punches and printing with edible ink.

X. Different types of tablets are available like buccal, floating, colon targeting, effervescent, dispersible, soluble, and chewable, etc.

XI. In composition to parenteral dosage form, a doctor or a nurse is not required for administration. I.e. self administration is possible.

XII. In comparison to capsules, tablets are more tamperproof.

XIII. Tablets are easy and convenient to use.

XIV. Tablets provide an accurately measured dosage in a convenient portable package, and can be designed to protect unstable medications or disguise unpalatable ingredients.

XV. Manufacturing processes and techniques can provide tablets special properties, for example enteric coatings or sustained release formulations**.**

1.3.5 Disadvantages of tablet as a dosage form.

I. Some drugs may be unsuitable for administration by the oral route.
II. Bioavailability of some drugs may be low due to poor absorption from the gastric tract. Such drugs may need to be given in very high doses or by injection.
III. It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
IV. Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.

1.3.6 Excipient and their functionalities.

Excipient means any component other than the active pharmaceutical ingredient(s) intentionally added to the formulation of a dosage form. Many guidelines exist to aid in selection of nontoxic excipients such as IIG (Inactive Ingredient Guide), GRAS (Generally Regarded as Safe), Handbook of Pharmaceutical Excipients and others. While selecting excipients for any formulation following things should be considered wherever possible: keep the excipients to a minimum in number minimize the quantity of each excipient and multifunctional excipients may be given preference over unifunctional excipients.

Excipients play a crucial role in design of the delivery system, determining its quality and performance. Excipients though usually regarded as nontoxic there are examples of known excipient induced toxicities which include renal failure and death from diethylene glycol, osmotic diarrhoea caused by ingested mannitol, hypersensitivity reactions from lanolin and cardio toxicity induced by propylene glycol.

Excipients are chosen in tablet formulation to perform a variety of functions like,

I. For providing essential manufacturing technology functions (Binders, glidants, lubricants may be added),
II. For enhancing patient acceptance (Flavors, colorants may be added),
III. For providing aid in product identification (Colorants may be added),

IV. For Optimizing or modifying drug release (Disintegrants, hydrophilic polymers, wetting agents, biodegradable polymers may be added),

V. For enhancing stability (Antioxidant, UV absorbers may be added)

Table 1. Various excipients used in tablet formulation and their functionalities.

EXCIPIENT	FUNCTION
Diluents or Fillers	Diluents make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size.
Binders or Granulating agents or Adhesives	Binders are added to tablet formulations to add cohesiveness to powders, thus providing the necessary bonding to form granules, which under compaction form a cohesive mass or a compact which is referred to as a tablet.
Disintegrants	A disintegrant is added to most tablet formulations to facilitate a breakup or disintegration of the tablet when placed in an aqueous environment.
Lubricants	Lubricants are intended to reduce the friction during tablet formation in a die and also during ejection from die cavity.
Antiadherents	Antiadherents are added to reduce sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall.
Glidants	Glidants are intended to promote the flow of tablet granulation or powder mixture from hopper to the die cavity by reducing friction between the particles.
MISCELLANEOUS	
Wetting agents	Wetting agents are added to tablet formulation to aid water uptake during disintegration and assist drug dissolution.
Dissolution retardants	Dissolution retardants as the name suggest, retards the dissolution of active pharmaceutical ingredient(s).
Dissolution enhancers	Dissolution enhancers as the name suggest, enhance the dissolution rate of active pharmaceutical ingredient(s).

Adsorbents	Adsorbents are capable of retaining large quantities of liquids without becoming wet; this property of absorbent allows many oils, fluid extracts and eutectic melts to be incorporated into tablets.
Buffers	Buffers are added to provide suitable micro environmental pH to get improved stability and / or bioavailability.
Antioxidants	Antioxidants are added to maintain product stability, they act by being preferentially oxidized and gradually consumed over shelf life of the product.
Chelating agents	Chelating agents are added to protect against autoxidation; they act by forming complexes with the heavy metal ions which are often required to initiate oxidative reactions.
Preservatives	Preservatives are added to tablet formulation in order to prevent the growth of micro-organisms.
Colours	Colours are added to tablet formulation for following purposes: to disguise off colour drugs, product identification and for production of more elegant product.
Flavours	Flavours are added to tablet formulation in order to make them palatable enough in case of chewable tablet by improving the taste.

2. AIM & OBJECTIVES

Due to various advantages of controlled release drug delivery system in present study, an attempt was made to formulate controlled release drug delivery system for Ibuprofen & to find the effect of different polymers such as stearic acid, glyceryl behnate and xanthan gum along with different excipients such as mannitol and dicalcium phosphate and with a view to obtain a better control over the release of the drug from the delivery system and for prolong the drug action in the therapeutic range and thereby reducing the dose frequency.

3. PLAN OF WORK

I. Active Pharmaceutical Ingredient (API) and excipients characterization to prepare solid oral dosage form of Ibuprofen controlled Release tablet.

II. To carry out preformulation studies.

a. Solubility.

b. Angle of repose.

c. Bulk density.

e. Tapped density.

f. Compressibility index.

g. Haussner's ratio.

III. To prepare and develop the dosage form of ibuprofen controlled Release tablet by wet granulation method.

IV. To evaluate the formulated tablets for their physicochemical characteristics such as:

a. Content uniformity.

b. Hardness.

c. Thickness.

d. Weight variation.

e. Friability.

V. *Invitro* Dissolution studies.

VI. Stability studies.

4. LITERATURE REVIEW

R. Patel et al. (2010)[6] reviewed ibuprofen, a weekly acidic, non-steroidal anti inflammatory drug having high permeability through stomach but due to its solubility limitation it can't enter in to systemic circulation and gastric empting time ranging from 30 min to 2 hr, after this time ibuprofen goes in to small intestine where it is solubilise but can't permeate through its membrane. To improve dissolution of such drug is challenging and rational. In present investigation, dissolution of ibuprofen improves by preparing floating granules. Floating is requiring for increasing residence time of granules in stomach. Ibuprofen must have to remain in stomach because it is mostly permeable through it. Multipurpose floating formulations was developed by preparing immediate release (for loading dose) granules containing gelucire 44/14 and sustained release floating granules containing gelucire 43/01 and small amount of gelucire 44/14. Amount of gelucire 44/14 and gelucire 43/01 was optimized using factorial design. Amount of gelucire 44/14 (X1) and amount of Gelucire 43/01 (X2) selected as independed variable. t100% (time require to dissolve 100 % drug) and total floating time chosen as response or depended variable. Release kinetic of ibuprofen studied by applying different model (zero order, first order, higuchi, korsmeyer-peppas, Hixson crowell and weibull). In optimized formulation, Granules remain floated for 3 hrs. and gave 100% drug release in 150 minute.

S. Chandran et. al. (2008)[7] studied Controlled release preparations have been reported to reduce the gastro irritant and ulcerogenic effects of non steroidal antiinflammatory drugs. In the present study, an attempt was made to develop matrix tablet-based controlled release formulations of ibuprofen, using ethyl cellulose as the rate-controlling polymer. In order to prevent initial release of the drug in the acidic environment of the stomach, cellulose acetate phthalate was incorporated in the matrix in varying amounts. It was found that with increasing the proportion of ethyl cellulose in the matrix, the drug release was extended for 14-16 h. Incorporation of cellulose acetate phthalate in ethyl cellulose matrix provided very low initial release of the drug in the first 2-3 h followed by enhanced release rate in alkaline medium owing to the high solubility of cellulose acetate phthalate at basic pH which led to

creation of a porous matrix. It was concluded that combination of cellulose acetate phthalate with ethyl cellulose in the matrix base can be an effective means of developing a controlled release formulation of ibuprofen with very low initial release followed with controlled release up to 14-16 h.

G.S. Sonar et al. (2007)[8] The purpose of this investigation was to prepared a gastroretentive floating drug delivery system (GFDDS) of the hydrophilic polymer hydroxy propyl methyl cellulose (HPMC), gas generating agent sodium bicarbonate and citric acid. A 32 factorial design was applied systematically; the amount of citric acid (X1) and amount of HPMC K100M (X2) were selected as independent variables. The time required for 50% drug release (t50%), percentage drug release at 12 hours (Q12) and percentage of drug release at 6 hours (Q6) were selected as dependent variables. The granules were prepared by wet granulation method and evaluated for their granules properties. The drug release from the tablets was sufficiently sustained followed the model controlled mechanism of tablet.

S.S. Krishna et al. (2006)[9] developed to extend the GI residence time of the dosage form and control the release of Ibuprofen using mucoadhesive tablet to achieve controlled plasma level of the drug which is especially useful after 8 to 12 weeks of monotherapy using conventional dosage forms when dose is doubled and plasma level also doubles. Direct compression method using simplex lattice design, Rosiglitazone maleate, Carbopol 934, Ethylcellulose (EC; 18-22 cP; Ethoxyl content 48-49.5%)andCellulose Acetate Phthalate followed by optimization of the evaluation parameters was employed to get final optimized formulation. The optimized formulation showed a mucoadhesive strength >40 gm-f, and a mucoadhesion time >12 hours with release profile closer to the target release.

M. H. Shoaib et al. (2005)[10] developed a once-daily sustained release matrix tablet of ibuprofen using hydroxypropyl methylcellulose (HPMC) as release controlling factor and to evaluate drug release parameters as per various release kinetic models. In order to achieve required sustained release profile tablets were directly compressed using Avicel pH 101 and Magnesium stearate. The formulated tablets were also characterized by physical and chemical parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for

selecting the most appropriate model was based on linearity (coefficient of correlation). The drug release data fit well to the Higuchi expression. Drug release mechanism was found as a complex mixture of diffusion, swelling and erosion.

P. Thapa et al. (2005)[11] formulated control release oral delivery system and to investigate the influence of different diluents, Carbopol 934P concentration and granulation technique in the release of poorly water-soluble drug (Ibuprofen) from Carbopol 934P matrix tablets. Matrix tablets were prepared by direct compression, wet granulation and dry granulation method at different polymer concentration using lactose, dibasic calcium phosphate (DCP), microcrystalline cellulose (MCC) and starch as diluents. Dissolution studies were carried out in 900 ml phosphate buffer pH 7.4 using USP-apparatus I. At 5% Carbopol 934P concentration, the $t_{50\%}$ was found in the rank order of tablets containing starch<MCC<DCP<lactose.

B. Arica et. al. (2005)[12] studied the irritation effects of ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID), were evaluated on mouse gastric and duodenal mucosa when suspended in 0.5% (w/v) sodium carboxy methylcellulose (NaCMC) solution and loaded in alginate beads. The ionotropic gelation method was used to prepare controlled release alginate beads of ibuprofen. The influence of various formulation factors on the encapsulation efficiency, as *in vitro* drug release and micromeritic properties, was investigated. Other variables included the alginate concentration, percentage drug loading and stirring speed during the microencapsulation process.

S.Turner et. al. (2005)[13] evaluated *in vitro* the release characteristics of a novel 600mg controlled release tablet formulation of ibuprofen using dissolution studies and in vivo human pharmacokinetic studies. In vitro analysis showed the formulation was capable of releasing ibuprofen in a controlled manner over 12 hours. In vivo analysis showed the formulation performed in a manner similar to that demonstrated by dissolution studies,

resulting in a biphasic profile of ibuprofen release. The available literature of ibuprofen suggests that such a biphasic profile is an appropriate rate of release for achieving the desired onset of action and prevention of breakthrough symptoms in vivo.

R. Canaparo et. al. (2000)[14] Described a specific method for the simultaneous determination of S-(+)Ibuprofen and R-(-)Ibuprofen enantiomers in human plasma. Adopting a high-performance liquid chromatographic (HPLC) system with spectrofluorometer detector, the compounds were extracted from plasma in alcohol medium and were separated on C18 column, using a solution of acetonitrile– water–acetic acid– triethylamine as mobile phase. The limit of quantitation was 0.1 mg/mL for both compounds. The method was validated by intra-day assays at three concentration levels and was used in a kinetic study in healthy volunteers. During the study we carried out inter-day assays to confirm the feasibility of the method.

M. Rafiee-Tehrani et al. (1999)[15] studied the need for controlled release (CR) formulations of ibuprofen tablet, is well recognized. The purpose of this study was to develop an air suspension method, using a laboratory scale fluidized bed drier to coat the ibuprofen granules. Different polymers including, Eudragits L100, S100, RL100, RS100, L100+S100 (1:1), RL100+RS100 (1:1), ethyl cellulose (EC) and Eudragit RS100+EC (1:1) were utilized. The drug release medium consisted of buffer pH 1.2 for 1st 2h, buffer pH 4.5 for 2nd 2h and buffer pH 7.5 for remaining period of time in all experiments, but the release behavior of the drug from some formulations was also studied using distilled water. Of the polymers investigated, Eudragit RS100, EC, Eudragit S100 and Eudragit RS100+EC (1:1) exhibited proper release characteristics when used as coating materials. The release patterns were analyzed from the standpoint of diffusion-controlled processes and as first-order kinetics.

5. MATERIALS & INSTRUMENTS USED.

Table 2. List of materials.

Sl. No.	Name of the ingredients	Category	Manufacturer
1	Ibuprofen	Drug	Matrix.lab's
2	Glyceryl behenate	Polymer	Signet chemicals
3	Xanthan gum	Polymer	Signet chemicals
4	Stearic acid	Polymer	Indchem international
5	Mannitol	Diluents	Colorcon
6	Dicalcium phosphate	Diluents	KMV Enterprises
7	Magnesium Stearate	Lubricant	Signet chemicals
8	Povidone K30	Binding agent	Signet chemicals
9	IPA(Iso propyl alcohol)	Solvent	Indchem international

Table 3. List of equipments.

Sl. No.	Equipment	Manufacturer
1.	Electronic balance	Citizen Pvt. Ltd,Mumbai
2.	Tapped density tester	Electro lab
3.	pH meter	Inolab
4.	Dissolution test apparatus	Electro lab USP
5.	UV-VISIBLE Spectrophotometer	Shimadzu
6.	Stability chambers	Thermo lab
7.	Hot air oven	Lab-shop corporation, Mumbai
8.	Monsanto hardness tester	Cadmach
9.	Roche friability tester	Labhosp, Mumbai
10.	Mesh	Retsec
11.	Mechanical stirrer	Remi motors , Bombay

5.1. DRUG PROFILE[16,17]

Drug name: IBUPROFEN

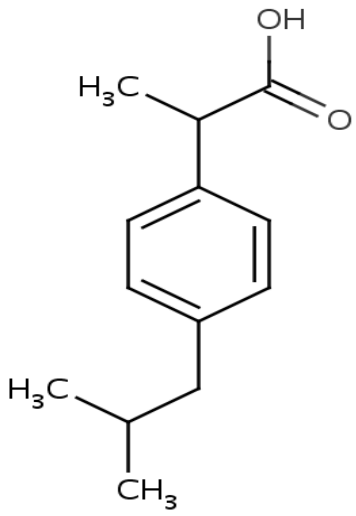

Fig 3. Chemical structure of (*RS*)-2-(4-(2-methylpropyl)phenyl)propanoic acid

CHEMICAL AND PHYSICAL PROPERTIES:

Molecular weight - 206.28.

Molecular formula - $C_{13}H_{18}O_2$.

Description - White or almost white, crystalline powder or colorless crystals.

Melting point - 76 °C (169 °F).

Molecular mass - 206.29 gm/mol.

Solubility - Insoluble in water, freely soluble in ethanol and chloroform**.**

PHARMACOKINETIC DATA[16,17].

Bioavailability - 49 – 73 %.

Protein binding – 99 %,

Metabolism – Hepatic.

Half-life – 1.8 - 2 h.

Excretion – Renal**.**

DOSE : 800mg-3200mg per day.

MECHANISM OF ACTION[18,19]

Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H_2 (PGH_2). PGH_2, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A_2 (Which stimulates platelet aggregation, leading to the formation of blood clots). Like aspirin, indomethacin, and most other NSAIDs, ibuprofen is considered a nonselective COX inhibitor; that is, it inhibits two isoforms of cyclo-oxygenase, COX-1 and COX-2. The analgesic, antipyretic, and anti-inflammatory activity of NSAIDs appears to be achieved mainly through inhibition of COX-2, whereas inhibition of COX-1 would be responsible for unwanted effects onplatelet aggregation and the gastrointestinal tract.[31] However, the role of the individual COX isoforms in the analgesic, anti-inflammatory, gastric damage effects of NSAIDs is uncertain and different compounds cause different degrees of analgesia and gastric damage. In order to achieve the beneficial effects of ibuprofen and other NSAIDS without gastrointestinal ulceration and bleeding, selective COX-2 inhibitors were developed to inhibit the COX-2 isoform without inhibition of COX-1**.**

ADVERSE EFFECTS[18].

Common adverse effects are nausea, dyspepsia, gastrointestinal ulceration/bleeding, raised liver enzymes, diarrhea, constipation, epistaxis, headache, dizziness, priapism, rash, salt, fluid retention, and hypertension. A study from 2010 has shown regular use of NSAIDs was associated with an increase in hearing loss. Infrequent adverse effects includes esophageal ulceration, heart failure, hyperkalemia, renal impairment, confusion, and bronchospasm. Ibuprofen appears to have the lowest incidence of digestive adverse drug reactions (ADRs) of all the nonselective NSAIDs. However, this holds true only at lower doses of ibuprofen, so OTC preparations of ibuprofen are, in general, labeled to advise a maximum daily dose of 1,200 mg**.**

PHOTOSENSITIVITY[18].

As with other NSAIDs, ibuprofen has been reported to be a photosensitising agent. However, this only rarely occurs with ibuprofen and it is considered to be a very weak photosensitising agent when compared with other members of the 2-arylpropionic acid class. This is because the ibuprofen molecule contains only a single phenyl moiety and no bond conjugation, resulting in a very weak chromophore system and a very weak absorption spectrum, which does not reach into the solar spectrum.

CARDIOVASCULAR RISK[18].

Along with several other NSAIDs, ibuprofen has been implicated in elevating the risk of myocardial infarction (Heart attack), in particular, among those chronically using high doses.

INTERACTIONS[18].

Drinking alcohol when taking ibuprofen increases risk of stomach bleeding. According to the U.S. Food and Drug Administration, ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg per day), potentially rendering aspirin less effective when used for cardioprotection and stroke prevention. Allowing sufficient time between doses of ibuprofen and immediate release aspirin can avoid this problem. The recommended elapsed time between a 400 mg dose of ibuprofen and a dose of aspirin depends on which is taken first. It would be 30 min or more for ibuprofen taken after immediate release aspirin, and 8 hours or more for ibuprofen taken before immediate release aspirin. However, this timing cannot be recommended for enteric-coated aspirin. But, if

ibuprofen is taken only occasionally without the recommended timing, the [reduction] of the cardioprotection and stroke prevention of a daily aspirin regimen is minimal.

ERECTILE DYSFUNCTION RISK[18].

A 2005 study linked long term (Over 3 months) use of NSAIDs, including ibuprofen, with a 1.4 times increased risk of erectile dysfunction.[21] [22] The report by Kaiser Permanente and published in the Journal of Urology, considered that "regular non-steroidal anti-inflammatory drug use is associated with erectile dysfunction beyond what would be expected due to age and other condition".[23] The director of research for Kaiser Permanente added that "There are many proven benefits of non steroidals in preventing heart disease and for other conditions. People shouldn't stop taking them based on this observational study. However, if a man is taking this class of drugs and has ED, it's worth a discussion with his doctor.

OVERDOSE[18,19].

Ibuprofen overdose has become common since it was licensed for OTC use. There are many overdose experiences reported in the medical literature, although the frequency of life-threatening complications from ibuprofen overdose is low.[24] Human response in cases of overdose ranges from absence of symptoms to fatal outcome in spite of intensive care treatment. Most symptoms are an excess of the pharmacological action of ibuprofen and include abdominal pain, nausea, vomiting, drowsiness, dizziness, headache, tinnitus, and nystagmus. Rarely, more severe symptoms such as gastrointestinal bleeding, seizures, metabolic acidosis, hyperkalaemia, hypotension, bradycardia, tachycardia, atrial fibrillation, coma, hepatic dysfunction, acute renal failure, cyanosis, respiratory depression, and cardiac arrest have been reported. The severity of symptoms varies with the ingested dose and the time elapsed; however, individual sensitivity also plays an important role. Generally, the symptoms observed with an overdose of ibuprofen are similar to the symptoms caused by overdoses of other NSAIDs**.**

There is little correlation between severity of symptoms and measured ibuprofen plasma levels. Toxic effects are unlikely at doses below 100 mg/kg, but can be severe above 400 mg/kg (around 150 tablets of 200 mg units for an average man);[26] however, large doses do not indicate the clinical course is likely to be lethal.[27] It is not possible to determine a precise lethal dose, as this may vary with age, weight, and concomitant diseases of the individual patient**.**

Therapy is largely symptomatic. In cases presenting early, gastric decontamination is recommended. This is achieved using activated charcoal; charcoal adsorbs the drug before it can enter the systemic circulation. Gastric lavage is now rarely used, but can be considered if the amount ingested is potentially life-threatening, and it can be performed within 60 min of ingestion. Emesis is not recommended. The majority of ibuprofen ingestions produce only mild effects and the management of overdose is straightforward. Standard measures to maintain normal urine output should be instituted and renal function monitored.[26] Since ibuprofen has acidic properties and is also excreted in the urine, forced alkaline diuresis is theoretically beneficial. However, because ibuprofen is highly protein-bound in the blood, there is minimal renal excretion of unchanged drug. Forced alkaline diuresis is, therefore, of limited benefit. Symptomatic therapy for hypotension, GI bleeding, acidosis, and renal toxicity may be indicated. On occasion, close monitoring in an intensive care unit for several days is necessary. If a patient survives the acute intoxication, he or she will usually experience no late sequelae**.**

DETECTION IN BODY FLUIDS[18,19].

Ibuprofen may be quantitated in blood, plasma, or serum to demonstrate the presence of the drug in a person having experienced an anaphylactic reaction, confirm a diagnosis of poisoning in hospitalized patients, or assist in a medicolegal death investigation. A nomogram that relates the ibuprofen plasma concentration, time since ingestion, and risk of developing renal toxicity in overdose patients has been published.

5.2 EXCIPIENTS PROFILE[20].

1. Stearic Acid.

1. Synonyms

Cetylacetic acid; Crodacid; E570; Edenor; Emersol; Hystrene; Industrene; Kortacid 1895;

Pearl Steric; Pristerene; stereophanic acid; Tegostearic.

2. Functional Category

Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

3. Applications in Pharmaceutical Formulation or Technology

Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used

in oral formulations as a tablet and capsule lubricant.Although it may also be used as a binder or in combination with shellac as a tablet coating.It has also been suggested that stearic acid may be used as a sustained-release drug carrier.In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation ofcreams. The partially neutralized stearic acid forms a creamy base when mixed with 5–15 times its own weight of aqueous liquid; the appearance and plasticity of the cream being determined by the proportion of alkali used.Stearic acid is used as the hardening agent in glycerin suppositories.

Stearic acid is also widely used in cosmetics and food products.

4. Description

Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a

white or yellowish white powder. It has a slight odor and taste suggesting tallow.

5. Solubility:

Freely soluble in benzene, carbon tetrachloride, chloroform, and ether; soluble in ethanol (95%), hexane, and propylene glycol; practically insoluble in water.

6. Stability and Storage Conditions

Stearic acid is a stable material; an antioxidant may also be added to it. The bulk material should be stored in a well-closed container in a cool, dry place.

7. Incompatibilities

Stearic acid is incompatible with most metal hydroxides and may be incompatible with oxidizing agents.Insoluble stearates are formed with many metals; ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salts.A number of differential scanning calorimetry studies have investigated the compatibility of stearic acid with drugs. Although such laboratory studies have suggested incompatibilities,e.g. with naproxen, they may not necessarily be applicable to formulated products.Stearic acid has been reported to cause pitting in the film coating of tablets coated using an aqueous film-coating technique; the pitting was found to be a function of the melting point of the stearic acid.

8. Safety

Stearic acid is widely used in oral and topical pharmaceutical formulations; it is also used in cosmetics and food products. Stearic acid is generally regarded as a nontoxic and nonirritant material. However, consumption of excessive amounts may be harmful.

2. GLYCERYL BEHENATE.

Non-proprietary names - BP: Glycerol dibehenate, PhEur: Glycerol dibehenate and USP-NF: Glyceryl behenate.

Synonyms - 2, 3-dihydroxypropyl docosanoate, 2, 3-dihydroxypropyl ester, glycerol behenate and glyceroli dibehenas.

Empirical Formula and Molecular Weight - Glyceryl dibehenate is a mixture of glycerol esters. The PhEur 6.0 describes glyceryl dibehenate as a mixture of diacylglycerols, mainly dibehenoyl glycerol, together with variable quantities of mono- and triacylglycerols. The USP32–NF27 describes glyceryl behenate as a mixture of glycerides of fatty acids, mainly behenic acid. It specifies that the content of 1-monoglycerides should be 12.0–18.0%.

Functional Category - Coating agent, tablet binder, tablet and capsule lubricant, thickening agent and viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology **-** Glyceryl behenate is used in cosmetics, foods, and oral pharmaceutical formulations. In pharmaceutical formulations, glyceryl behenate is mainly used as a lubricant in the preparation of oral tablets and capsules. It has good binding properties, it does not affect tablet hardness and is unaffected by mixing or production parameters. Glyceryl behenate has been investigated for the encapsulation of various drugs such as retinoids. It has also been investigated for use in the preparation of sustained-release tablets as a matrix-forming agent for the controlled release of water-soluble drugs, and it can also be used as a hot-melt coating agent sprayed onto a powder or drug-loaded sugar beads and granules. It may also be incorporated via extrusion/spheronization into pellets, which can be further compressed into tablets. Glyceryl behenate is used in oral enteric-coated pellets, powders and suspensions. It is also used in controlled, extended-release and orally disintegrating tablets. For oral preparations, glyceryl behenate forms a lipidic matrix for sustained-release formulations. It has been used along with acid-soluble or swellable polymers to mask the bitter or unpleasant taste of the medicament with improved palatability. Glyceryl behenate has been used for the preparation of ophthalmic inserts. In cosmetics, glyceryl behenate is used as a skin conditioning agent, emollient and viscosity increasing agent in emulsions. It also improves the heat stability of emulsions and is a gelifying agent for various oils. For topical formulations, it is used as a thickening agent for oily phases. It is also used as a surfactant or emulsifying agent.

Uses of glyceryl behenate -

Use	**Concentration (%)**
Lipophilic matrix or coating for sustained-released	
Tablets and capsules	>10.0
Tablet and capsule lubricant	1.0–3.0
Viscosity-increasing agent in silicon gels (cosmetics)	1.0–15.0
Viscosity increasing agent in w/o or o/w emulsions	1.0-5.

Description - Glyceryl behenate occurs as a fine white-yellow powder, as a hard waxy mass or pellet and as white or almost white unctuous flakes. It has a faint odor.

Solubility - Soluble when heated in chloroform and dichloromethane, also in many organic solvents, slightly soluble in hot ethanol (96%), practically insoluble in cold ethanol (95%), hexane, mineral oil and water.

Stability and Storage Conditions - Glyceryl behenate should be stored in a tightly closed container, at a temperature less than 35°C**.**

3.Xanthan gum

Nonproprietary Names: BP: Xanthan gum,PhEur: Xanthani gummi,USPNF: Xanthan gum

Synonyms:

Corn sugar gum, polysaccharide , Xantura, Xanthan gum

Empirical Formula and Molecular Weight(C35H49O29)n Approximately 2 _ 106.The USPNF 23 describes xanthan gum as a high molecularweight polysaccharide gum. It contains D-glucose and Dmannoseas the dominant hexose units, along with Dglucuronic acid, and is prepared as the sodium, potassium, or

calcium salt.

Functional Category: Stabilizing agent; suspending agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulationor Technology: Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range;

Xanthan gum gels show pseudoplastic behavior,the shear thinning being directly proportional to the shear rate.The viscosity returns to normal immediately on release of shear stress. When xanthan gum is mixed with certain inorganic suspending agents, such as magnesium aluminum silicate, or organic gums, synergistic rheological effects occur. In general, mixtures of xanthan gum and magnesium aluminum silicate in ratios between 1 : 2 and 1 : 9 produce the optimum properties.Similarly, optimum synergistic effects are obtained with xanthan gum : guar gum ratios between 3 : 7 and 1 : 9.Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets.Controlled-release tablets of diltiazem hydrochlorideprepared using xanthan gum have been reported to sustain the drug release in a predictable manner and the drug release profiles of these tablets were not affected by pH and agitation rate. Xanthan gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin, thereby helping in the prolonged retention of the dosage form in the precorneal area.Recent studies have revealed that xanthan gum can also be used as an excipient for spray-drying and freeze-drying processes for better results.Xanthan gum can be used to increase the bioadhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems. Xanthan gum is also used as a hydrocolloid in the food industry, and in cosmetics it has been used as a thickening agent in shampoo.

Description:

Xanthan gum occurs as a cream- or white-colored, odorless,free-flowing, fine powder.

Pharmacopeial Specifications

Table I: Pharmacopeial specifications for xanthan gum.

Test PhEur 2005 USPNF 23

Identification þ þ

Characters þ —

pH 6.0–8.0 —

Viscosity 5600 mPas 5600 mPas

Propan-2-ol 4750 ppm 40.075%

Other polysaccharides þ —

Loss on drying 415.0% 415.0%

Total ash 6.5–16.0% 6.5–16.0%

Microbial contamination þ þ

Bacteria 4103/g —

Fungi 4102/g —

Pyruvic acid — 41.5%

Arsenic — 43 mg/g

Lead — 45 mg/g

Heavy metals — 40.003%

Organic volatile impurities — þ

Assay — 91.0–108.0%

10 Typical Properties

Acidity/alkalinity: pH = 6.0–8.0 for a 1% w/v aqueous

solution.

Freezing point: 08C for a 1% w/v aqueous solution.

Heat of combustion: 14.6 J/g (3.5 cal/g)

Melting point: chars at 2708C.

Particle size distribution: various grades with different particle sizes are available; for example, 100% less than 180 mm in size for Keltrol CG; 100% less than 75 mm in size for

Keltrol CGF; 100% less than 250 mm, 95% less than 177 mm in size for Rhodigel; 100% less than 177 mm, 92% less than 74 mm in size for Rhodigel 200.

Refractive index: nD 20 = 1.333 for a 1% w/v aqueous solution.

Solubility: practically insoluble in ethanol and ether; soluble in cold or warm water.

Specific gravity: 1.600 at 258C

Viscosity (dynamic): 1200–1600 mPa s (1200–1600 cP) for a1% w/v aqueous solution at 258C.

Stability and Storage Conditions: Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–608C.

Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Solutions are also stable in the presence of enzymes, salts, acids, and bases. The bulk material should be stored in a well-closed container in a cool, dry place.

Safety: Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient. The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body-weight.(22)

LD50 (dog, oral): >20 g/kg(22)

LD50 (rat, oral): >45 g/kg

LD50 (mouse, oral): >1 g/kg(23)

LD50 (mouse, IP): >50 mg/kg(23)

LD50 (mouse, IV): 100–250 mg/kg

Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

Regulatory Status: GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral solutions, suspensions, and tablets; rectal and topical preparations).

Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinalIngredients.

Related Substances: Ceratonia; guar gum.

4. MANNITOL.

Non-proprietary names - BP: Mannitol, JP: D-Mannitol, PhEur: Mannitol and USP: Mannitol.

Synonyms - Cordycepic acid, C*PharmMannidex, E421, emprove, manna sugar, D-mannite, mannite, mannitolum, mannogem and pearlitol.

Chemical name and CAS Registry Number - D-Mannitol [69-65-8].

Empirical Formula and Molecular Weight - $C_6H_{14}O_6$ and 182.17.

Functional Category - Diluent, plasticizer, sweetening agent, tablet and capsule diluent, therapeutic agent, tonicity agent.

Applications in Pharmaceutical Formulation or Technology **-** Mannitol is widely used in Pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients. Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'. In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. A pyrogen-free form is available specifically for this use. Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminium hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carrier in dry powder inhalers. It is also used as diluents in rapidly dispersing oral dosage forms. It is used in food applications as a bulking agent. Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure. Given orally, mannitol is not absorbed significantly from the gastrointestinal tract, but in large doses it can cause osmotic diarrhea.

Description - Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

Solubility of mannitol -

Solvent	Solubility at 20C
Alkalis	Soluble
Ethanol (95%)	1 in 83
Ether	Practically insoluble
Glycerine	1 in 18
Propan-2-ol	1 in 100
Water	1 in 5.5

Stability and Storage Conditions - Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions. The bulk material should be stored in a well-closed container in a cool, dry place**.**

4. DICALCIUM PHOSPHATE (DCP).

Nonproprietary names - BP: Calcium hydrogen phosphate, JP: Dibasic calcium phosphate, PhEur: Calcii hydrogenophosphas dihydricus and USP: Dibasic calcium phosphate.

Synonyms - Calcium hydrogen orthophosphate dihydrate; calcium monohydrogen phosphate dihydrate; Di-Cafos; dicalcium orthophosphate; DI-TAB; E341; Emcompress; phosphoric acid calcium salt (1 : 1) dihydrate; secondary calcium phosphate.

Chemical name - Dibasic calcium phosphate dihydrate.

Empirical Formula and Molecular Weight - $CaHPO_4\_2H_2O$ and 172.09.

Functional Category - Tablet and capsule diluents.

Applications in Pharmaceutical Formulation or Technology - Dibasic calcium phosphate dihydrate is widely used in tablet formulations both as an excipient and as a source of calcium and phosphorus in nutritional supplements. It is one of the more widely used materials, particularly in the nutritional/ health food sectors. It is also used in pharmaceutical products because of its compaction properties, and the good flow properties of the coarse-grade material. Dibasic calcium phosphate dihydrate is abrasive and a lubricant is required for tableting, for example about 1% w/w of magnesium stearate or about 1% w/w of sodium stearyl fumarate is commonly used.

Typical Properties - Acidity/alkalinity: pH = 7.4 (20% slurry of DI-TAB).

Angle of repose: 28.38 for Emcompress.

Density (bulk): 0.915 gm/cc.

Density (tapped): 1.17 gm/cc.

Density (true): 2.389 gm/cm^3.

Melting point: dehydrates below 100°C.

Solubility -Practically insoluble in ethanol, ether, and water. Soluble in dilute acids.

Stability and Storage Conditions - Dibasic calcium phosphate dihydrate is a non hygroscopic, relatively stable material. However, under certain conditions the dihydrate can lose water of crystallization. This has implications for both storage of the bulk material and coating and packaging of tablets containing dibasic calcium phosphate dihydrate. The bulk material should be stored in a well-closed container in a cool, dry place**.**

5. MAGNESIUM STEARATE.

Non-proprietary names - BP: Magnesium stearate, JP: Magnesium stearate, PhEur: Magnesii stearas.

Synonyms - Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical Name - Octadecanoic acid magnesium salt.

Empirical Formula and Molecular Weight - $C_{36}H_{70}MgO_4$ and 591.34.

Description - The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

Structural Formula - $[CH_3 (CH_2)_{16}COO]_2Mg$.

Functional Category - Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology - Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 and 5.0% w/w. It is also used in barrier creams. Description magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Crystalline forms - high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate and an anhydrate.

Density (bulk): 0.159 gm/cm^3.

Density (tapped): 0.286 gm/cm^3.

Density (true): 1.092 gm/cm^3.

Flash point: 250°C.

Flow ability: poorly flowing, cohesive powder.

Melting range: 117–150°C (Commercial samples),

126–130C (High purity magnesium stearate).

Solubility - Practically insoluble in ethanol, ethanol (95%), ether and water. Slightly soluble in warm benzene and warm ethanol (95%).

Stability and Storage Conditions - Magnesium stearate is stable and should be stored in a well closed container in a cool and dry place**.**

6. ISOPROPYL ALCOHOL.

Non-proprietary names - BP: Isopropyl alcohol, JP: Isopropanol, PhEur: Isopropyl alcohol, USP: Isopropyl alcohol.

Synonyms -Alcohol isopropylicus, dimethyl carbinol, IPA, isopropanol, petrohol, 2-propanol, sec-propyl alcohol and rubbing alcohol.

Empirical Formula and Molecular Weight - C_3H_8O and 60.1.

Functional Category - Disinfectant and solvent.

Applications in Pharmaceutical Formulation or Technology -Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations. It is not recommended for oral use owing to its toxicity; although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation,(2) where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide from carbomer. Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

Typical Properties - Antimicrobial activity Isopropyl alcohol is bactericidal; at concentrations greater than 70% v/v it is a more effective antibacterial preservative than ethanol (95%). The bactericidal effect of aqueous solutions increases steadily as the concentration approaches 100% v/v. Isopropyl alcohol is ineffective against bacterial spores.

Autoignition temperature is 425°C. Boiling point 82.4°C. Dielectric constant D20 = 18.62.

Explosive limits 2.5–12.0% v/v in air. Flammability Flammable: Flash point 11.7°C (closed cup), 138°C (open cup). The water azeotrope has a flash point of 16°C.

Melting point - 88.5°C. Moisture content is 0.1–13% w/w for commercial grades (13% w/w corresponds to the water azeotrope). Solubility: Miscible with benzene, chloroform, ethanol (95%), ether, glycerin and water. Soluble in acetone and insoluble in salt**.**

7. POVIDONE.

Synonyms - Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene], polyvidone; polyvinyl pyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Chemical name - 1-Ethenyl-2-pyrrolidinone homopolymer

Empirical formula - (C_6H_9NO) n

Molecular Weight - 2500–3000000.

Functional Category - Disintegrant; dissolution aid; suspending agent; tablet binder

Description - Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidone with K-values equal to or lower than 30 are manufactured by Spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

Solubility - Freely soluble in acids, chloroform, ethanol (95%),ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Stability and storage - Povidone is stable. However it is a hygroscopic material. It should be stored in airtight container cool and dry place.

Applications - In tableting, povidone solutions are used as binders in wet granulation processes. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents as a carrier for the drugs (10-25%); as binder (0.5- 5%). Suspending and viscosity builder up to 5%**.**

6. EXPERIMENTAL SECTION

PREPARATION OF pH 7.2 PHOSPHATE BUFFER:

Place 50ml of 0.2M potassium dihydrogen phosphate in 200ml of volumetric flask and specified volume 0.2M NaoH (34.7ml) make up to volume.

0.2M Potassium dihydrogen phosphate:

Dissolve 27,218gm of potassium dihydrogen phosphate in water and dilute with water to 1000ml.

0.2M Sodiumhydroxide (NaoH):

Dissolve NaoH in water to produce a 40 to 60 percent w/v solution and allow to stand.Taking precautions to avoid the absorption of CO_2 siphon off the clear supernatant liquid and dilute with carbondioxide free water a sutible volume of the liquid containing 8gm of NaoH IN 1000ml.

PREPARATION OF STANDARD CURVE FOR IBUPROFEN:

Accurately 100 mg of pure drug was weighed and it taken in 100 ml volumetric flask. The drug was dissolved in 100ml of phosphate buffer pH-7.2 in a 100 ml volumetric flask. Now the solution was shaked till the drug dissolved completely. Then the primary solution was kept for 30 min and the solution was then filtered. From this primary solution, 10 ml of solution was taken in another 100 ml volumetric flask and the solution was then diluted with phosphate buffer pH-7.2 and the volume was adjusted up to 100 ml. From this stock solution, 1.0, 2.0, 3.0, 4.0, 5.0 and 6.0 ml were taken in a 10 ml volumetric flask. These solutions were diluted with phosphate buffer pH-7.2 up to 10 ml. Absorbance studies of all the solutions were carried out by using UV-Visible spectrophotometer at λ_{max} 221 nm is given in Table 11. The regression equation obtained from the graph plotted by taking absorbance vs concentration was y = 0.0045x - 0.0001, with regression co-efficient value is 1.00, as represented in Fig 4.

Table 4. Standard curve of ibuprofen in phosphate buffer pH 7.2.

Sl. No.	Concentration (µg/ml)	Absorbance
1	10	0.045
2	20	0.09
3	30	0.136
4	40	0.181
5	50	0.226
6	60	0.271

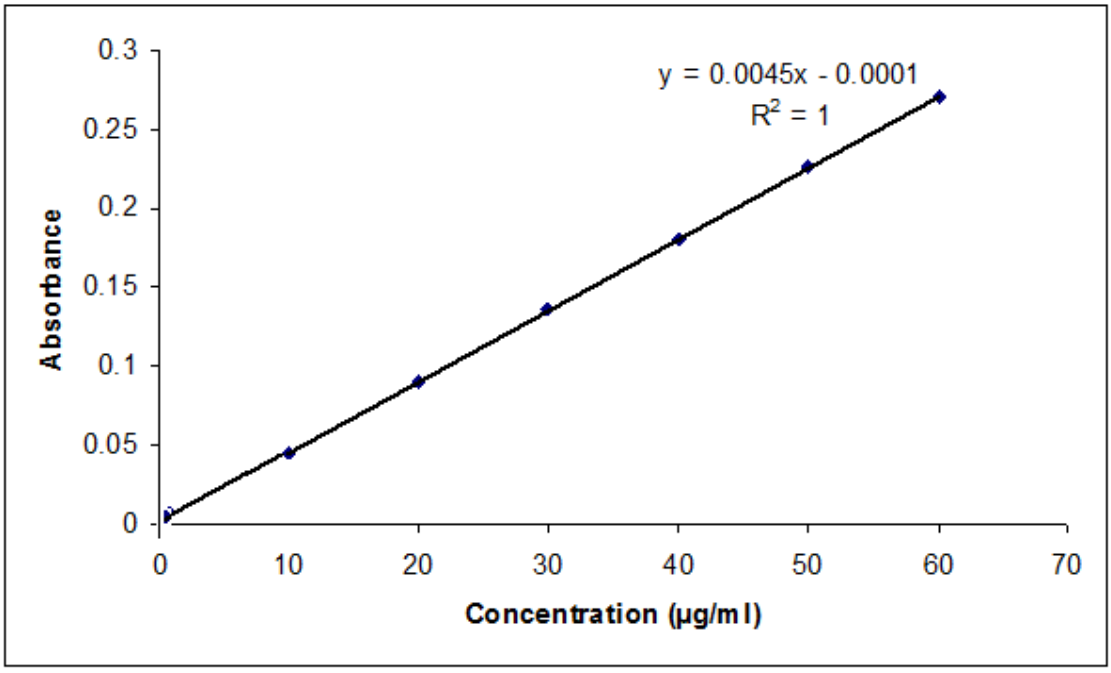

Fig 4. Calibration curve of ibuprofen pure drug in phosphate buffer pH 7.2.

METHODOLOGY.

Preformulation studies[16,17].

Preformulation activities range from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of dosage form. Critical information provided during preformulation can enhance the rapid and successful introduction of new therapeutics entities for humans. Preformulation 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 form.

The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bioavailability. Further the use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. For any drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, bulk density, tapped density, compressibility, molecular weight, sieve analysis**.**

1. PHYSICAL APPEARANCE:

A small quantity of ibuprofen was taken in butter paper and viewed in well illuminated place. Finally the colour, odour and texture were observed.

2. SOLUBILITY[21,22]:

A semi-quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition, the system vigorously shaken and examined visually for any undissolved solute particles. The solubility was expressed in terms of ratio of solute and solvent**.**

3. BULK DENSITY[21,22]:

A bulk density is defined as the ratio of mass of the drug and its bulk volume. Exactly 50 gm of drug were weighed on digital balance and transferred into a 100 ml measuring cylinder. The volume occupied by the drug was recorded as the bulk volume. This is the bulk

volume and the bulk density was calculated. It is expressed in gm/cc and is given by, Db (gm/cc) $= \frac{M}{Vb}$, Where, M is the mass of drug in gm and Vb is the bulk volume of the drug**.**

4. TAPPED DENSITY[21,22]:

Tapped densities of drug are defined as the ratio of mass of the drug and its tapped volume.

Exactly 50 gm of pure drug were weighed on digital balance and transferred into a 100 ml measuring cylinder. The cylinder was tapped on the wooden platform until the volume occupied by the drug remained constant. This is the tapped volume and the tapped density was calculated. It is expressed in g/cc and is given by, Tb (gm/cc) $= \frac{M}{Vt}$, Where, M is the mass of drug in gm and Vt is the bulk volume of the drug**.**

Tapped density = Wt. of sample in gm / Tapped volume

5. COMPRESSIBILITY INDEX[21,22]:

It indicates powder flow properties. It is expressed in percentage by comparing the bulk density and tapped density. A useful empirical guide is given by Carr's compressibility[3]**.**

$$\text{Carr's Index } (\%) = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Table 5. Carr's Index and flow property relationship.

Sl. No.	Carr's Index	Properties
1	5-12	Free flowing
2	12-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

6. HAUSNERS RATIO[21,22]:

Hausner's Ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. It is measured by the ratio of tapped density to the bulk density**.** Hausner's Ratio = $\frac{\text{Tapped density}}{\text{Bulk density}}$

Table 6. Hausner's ratio and flow property relationship.

Sl. No.	Hausner's Ratio	Property
1	<1.25	Better flow ability
2	>1.25	Poor flow ability

7. ANGLE OF REPOSE[21,22]:

Angle of repose was determined by fixed funnel method. Funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip at a given height (H) above a graph paper placed on a flat horizontal surface. About 50 gm of the drug were placed in a plugged glass funnel which had a distance of 10 cm from the surface. The drug was then allowed to flow through the 8 mm funnel orifice by removing the cotton plug from the funnel orifice. The height of the heap (h) formed as well as the radius of the heap (r) was noted**.** The angle of repose (θ) was calculated as $\theta = \tan^{-1} h/r$.

Table 7. Angle of repose and flow property relationship.

Angle of repose (^{0})	Powder flow
< 26	Excellent
26 – 30	Good
30 – 40	Passable
> 40	Very poor

Drug excipient compatibility studies[16]:

The compatibility studies are carried out to study the possible interactions between ibuprofen and inactive ingredients. Physical mixtures of ibuprofen and excipients in different ratio are prepared and kept for stability at $40^0C\pm2^0/75\%\pm5\%$ RH for one month. Samples are subjected to physical (Colour, appearance) and chemical testing (Assay of ibuprofen and impurities).

The compatibility studies are carried out by taking a mixture of drug and excipients at the ratio in which they are expected to be present in the innovator product. A part of mixture can be exposed to different storage conditions like $40^0C\pm2^0/75\%\pm5\%$ RH and control samples are to be kept at 2-8^oC. They are tested with respect to their physical and chemical aspects**.**

Table 8. Composition of Ibuprofen controlled release tablets.

Ingredients (mg)	**Formulations**					
	F1	F2	F3	F4	F5	F6
Ibuprofen	600	600	600	600	600	600
Stearic acid	100	100	-	-	-	-
Glyceryl behanate	-	-	100	100	-	-
Xanthan gum	-	-	-	-	250	250
Mannitol	265	-	265	-	115	65
DCP	-	265	-	265	-	50
Povidone K30	25	25	25	25	25	25
IPA	Qs	Qs	Qs	Qs	Qs	Qs
Magnesium Stearate	10	10	10	10	10	10
Total tablet weight	1000	1000	1000	1000	1000	1000

Qs Denotes quantity sufficient.

Granulation and compression for manufacturing of ibuprofen control release tablets:

Here the drug is homogenously dispersed throughout a rate controlling medium. Hydrophobic and hydrophilic matrices are used to control the release of the drug having different solubility properties. The drug Ibuprofen was selected for the formulation of matrix tablets. Different polymers like stearic acid, glyceryl behanate, xanthan gum with other

excipients like mannitol, DCP & lubricants like magnesium stearate were used in all the formulations. All the formulations were formulated by wet granulation method. The procedure employed for each formulation is given below.

Accurately weighed quantities of ingredients along with drug mentioned in Table 7 were passed through sieve No. 60. All the ingredients, except lubricant (Magnesium stearate) and binder povidone K30, were manually blended homogeneously in a mortar by way of geometric dilution. The mixture was moistened with solution of 10% (W/V) povidone K30, isopropyl alcohol, granulated and passed through sieve No. 16 and dried in a hot air oven at 60 ^{0}C for sufficient time (3 to 4 h) so that the moisture content of the granules reached 2–4%. The dried granules were passed through sieve No. 44 and blended with magnesium stearate. The homogeneous blend was then compressed into tablets using capsule shaped punches of size 14 mm**.**

CHARACTERIZATION OF GRANULES:

1. BULK DENSITY.

Exactly 50 gm of granules were weighed on digital balance and transferred into a 100 ml measuring cylinder. The volume occupied by the granules was recorded as the bulk volume. This is the bulk volume and the bulk density was calculated. It is expressed in g/cc and is given by, Db (gm/cc) $= \frac{M}{Vb}$, Where, M is the mass of drug in gm and Vb is the bulk volume of the granules**.**

2. TAPPED DENSITY.

Exactly 50 gm of granules were weighed on digital balance and transferred into a 100 ml measuring cylinder. The cylinder was tapped on the wooden platform until the volume occupied by the drug remained constant. This is the tapped volume and the tapped density was calculated. It is expressed in g/cc and is given by, Tb (g/cc) $= \frac{M}{Vt}$, Where, M is the mass of drug in gm and Vt is the bulk volume of the drug**.**

3. COMPRESSIBILITY INDEX.

It is expressed in percentage by comparing the bulk density and tapped density. A useful empirical guide is given by Carr's compressibility**.**

$$\text{Carr's Index (\%)} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

4. HAUSNERS RATIO.

It is measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

5. ANGLE OF REPOSE.

Angle of repose was determined by fixed funnel method. Funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip at a given height (H) above a graph paper placed on a flat horizontal surface. About 50 gm of the drug were placed in a plugged glass funnel which had a distance of 10 cm from the surface. The drug was then allowed to flow through the 8 mm funnel orifice by removing the cotton plug from the funnel orifice. The height of the heap (h) formed as well as the radius of the heap (r) was noted[33,34]**.** The angle of repose (θ) was calculated as $\theta = \tan^{-1} h/r$.

Evaluation of tablets:

1. THICKNESS.

The thickness of tablets will be the only dimensional variable related to the process. About 10 tablets were measured for their thickness and diameter with a slide calliper, thickness Gauge. Average thickness and diameter were calculated**.**

2. WEIGHT VARIATION.

The USP weight variation test was done by weighing 20 tablets individually, the average weight was then calculated and comparing the individual tablet weights to the average weight. The tablets met the USP tests that were not more than 2 tablets were outside the percentage limit and no tablets differed by more than 2 times the percentage limit.

3. CONTENT UNIFORMITY.

About 20 tablets were selected randomly from each formulation, weighed. The weighed tablets were powdered. The powder equivalent to 100 mg of diclofenac sodium was accurately weighed and dissolved in phosphate buffer pH 7.2. After suitable dilution, the solution was analyzed for drug content by using UV-Visible spectrophotometer at 221 nm**.**

4. FRIABILITY.

The friability of tablets was determined by Roche Friabillator. About 20 tablets were taken and weighed. After weighing, the tablets were placed in the Roche Friabillator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for min dropping the from a distance of six inches with each revolution. After operation the tablets were de-dusted and reweighed.

Friability is determined by $F=100(W_0-W_t/W_0)$, Where, Wo = weight of tablets before friability test, Wt = weight of tablets after friability test.

5. HARDNESS TEST:

Hardness of the tablets was determined by Monsanto Hardness Tester and the hardness should be found within the range of 3.5-5.5 Kg/cm².

Invitro dissolution studies[24]:

The dissolution was carried out for different experimental trials and also for the innovator. The various results obtained were tabulated. Dissolution studies are carried out in the following media

Dissolution parameters:

Medium : 7.2 pH phosphate buffer.

Quantity : 900 ml.

Apparatus : USP apparatus II (paddle).

RPM : 50 rpm

Temperature : 37ºC ± 0.50c

Time intervals : 1hr,2hr,and up to24 hrs.

Calculation:

$$\textbf{Factor: -}\ \frac{1}{A_S} \times \frac{W_1}{100} \times \frac{5}{5} \times \frac{500}{L.C} \times \frac{P_1}{100} \times 100$$

W_1 = weight of working Standard

L.C= Label claim in mg

P_1 = % potency of working Standard

A_S = Absorbance of standard

STABILITY STUDY[25].

To asses the stability against temperature and light, optimized tablet formulation of ibuprofen were stored at storage condition of 40°C /75% RH for three months and various parameters like avg. weight, hardness, thickness, friability and drug content was determined periodically with 1 month interval. The study was continued up to three months.

7. RESULTS AND DISCUSSION

In process of pursuing the objective of control release drug delivery system; this research was aimed towards the formulation development of control release tablet for oral use to provide sustained release of ibuprofen for prolong period of time.

1. PREFORMULATION STUDIES.

The ibuprofen was white in colour, odourless, bitter in taste and powdery in appearance.

Table 9.Solubility values of crude drug in different solvent

S.No	Solvent	Solubility(mg/ml)
1	Water	0.01
2	Acetone	0.12
3	Ethanol	0.25
4	Chloroform	0.18
5	phosphate buffer pH 7.2	0.9

The bulk density of the powder was found to be 1.123 gm/cc. The tapped density of the powder was found to be 1.273 gm/cc. The Carr's Index was found to be 11.783 indicating good flow properties. The Hausner's ratio was found to be 1.133 and the value was indicating better flow properties.The angle of repose was obtained as 27.22°, indicating good flow of powder drug.

Table 10.Preformulation studies of Ibuprofen

S.No	**Parameter**	**Result**
1	Bulk density	1.123gm/cc
2	Tapped density	1.273gm/cc
3	Carr's index	11.783%
4	Haussner's ratio	1.133
5	Angle of repose	27.22°

2 Drug excipient compatibility studies.

Table 11. Drug–excipients compatibility studies.

Sl. No.	Excipients	Ratio	Description		Compatibility status
			Initial	Final	
1	Ibuprofen	-	White to off white powder	White to off white powder	Compatible
2	API – DCP	1:20	Off white coloured powder	Off white coloured powder	compatible
3	API – Mannitol	1:20	Off white colored powder	Off white coloured powder	compatible
4	API – Glyceryl dibehenate	1:5	Off white coloured powder	Off white coloured powder	compatible
5	API – Magnesium stearate	1:0.25	Off white colored powder	Off white colored powder	compatible
6	API – Stearic acid	1:5	Off white colored powder	Off white colored powder	Compatible
7	API – Xanthan gum	1:10	Off white colored powder	Off white colored powder	Compatible

The result of drug excipient compatibility study is represented in Table 11. It could be concluded from the result of drug excipient compatibility study, there no such physical interaction are there between drug and excipient explaining, drug and excipient were compatible with each other for designing of control release tablet of ibuprofen.

3 Characterization of granules.

Table 12. Flow properties data of various granule formulations containing ibuprofen.

Formulation	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility index (%)	Hausner's ratio	Angle of repose (°)	Flow comment
F_1	0.54	0.64	15.625	1.185	26.67	Good
F_2	0.52	0.65	20.001	1.250	25.87	Good
F_3	0.56	0.67	16.417	1.196	27.08	Good
F_4	0.45	0.54	16.667	1.200	28.98	Good
F_5	0.46	0.57	19.298	1.239	26.66	Good
F_6	0.49	0.59	16.949	1.204	29.12	Good

The result of flow properties of prepared granules of various formulations of ibuprofen is given in Table 12. Flow properties of the granules, resistance to particle movement can be judged from the bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading as might be applied in mixing and tabletting. The bulk density was found within the range of 0.42 to 0.56 g/cc. The tapped density was found within the range of 0.54 to 0.67 g/cc. Using the density data, Hausner's ratio and Carr's index was calculated. The Hausner's ratio was found within the ranges of 1.185 to 1.250 which indicates better flowability. The Carr's index was found within the ranges of 15.625 to 20.001, explaining good flow properties. The angle of repose was found using fixed funnel method, which is within the ranges of 26.67 to 29.12, indicating good flow properties.

4 Evaluation data of control release tablet of ibuprofen.

Table 13. Physicochemical properties of prepared tablet formulations.

Formulations	Avg. wt. (mg)	Thickness (mm)	Hardness Kg/cm^2	Drug content (%)	Friability (%)
F_1	980	2.4	4	98.4	0.013
F_2	978	2.6	3.5	99.5	0.025
F_3	980	2.8	5	97.2	0.023
F_4	995	2.5	4	98.9	0.019
F_5	975	2.3	4.5	98.2	0.022
F_6	979	2.7	4	98.8	0.018

The tablets of various formulations were subjected to various evaluation tests, such as thickness, weight variation, friability, hardness, and drug release rate by dissolution studies according to the procedure specified in the I.P. All formulations are found to be satisfactory.

The physical examination of tablets showed that the tablets were circular or round in shape. The studies also indicated that there were no cracks on the tablets. The data indicates that all the formulations were good.

The thickness of each batch tablets of all formulations was determined and the results presented in Table 13. Thickness of tablets was found to be almost uniform in all the six formulations. They were found to be in the ranges of 2.3 to 2.8 mm.

The weight variation test (%) was conducted for each batch formulations (n=10) as per I.P and the results are shown in the Table 13. All the tablets passed weight variation test as the % weight variation, which was within the Pharmacopoeial limits of ± 5% of the weight. The average weight of all tablet formulations was within the ranges of 975 to 995 mg. The weights of all the tablets were found to be almost uniform.

The adequate tablet hardness is the necessary requisite for consumer acceptance and handling. The measured hardness of tablets of each batch of all formulations was ranged between 3.5 to 5 Kg/cm^2, which is falling within the hardness specification as per I.P.

The friability test for tablet formulations was done as per the standard procedure of I.P. The results of friability test were tabulated in Table 13. The friability of tablets within the ranges between 0.013 to 0.025, which are generally considered and acceptable as per I.P. The data indicates that the percentage friability was less than 1% in all the formulations ensuring no physical damage will be take place during handling and shipping of tablets.

The drug content of each formulation was evaluated as per the standard protocol and the results are shown in Table 13. The results indicate that the percentage of drug content was within the ranges of 97.2 to 99.5 % of paracetamol which was within the acceptable limits as per the I.P

Invitro Dissolution studies:

Table 14. *In vitro* drug release profile of various control release tablet formulations.

Sl. No.	Time (h)	Cumulative percentage of drug Release					
		F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	1	25	19	23	21	30	26
2	2	30	25	31	28	42	38
3	4	42	31	41	35	54	45
4	5	50	39	53	42	65	54
5	6	55	43	60	48	75	62
6	8	62	49	70	59	89	76
7	10	70	57	82	67	91	84
8	12	77	63	89	75	93	91
9	16	86	68	94	82	97	95
10	24	96	74	98	91	99	99

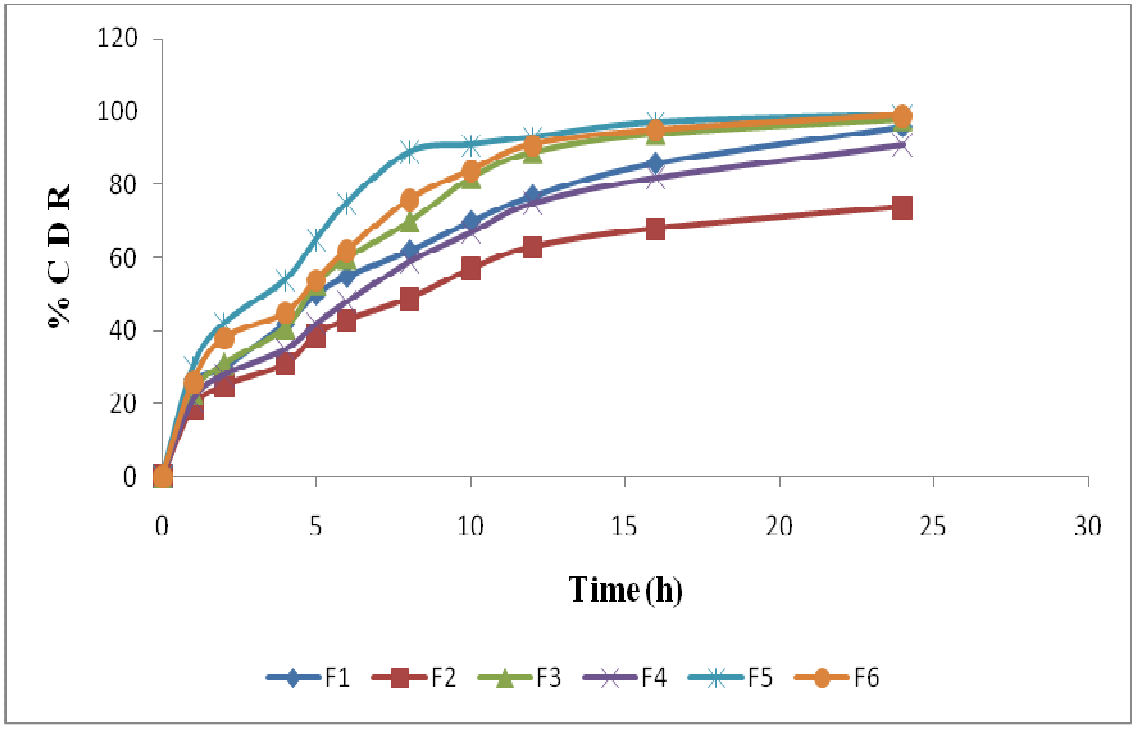

Fig 5. ***In vitro*** **drug release profile of various control release tablet formulations.**

% C D R: Cumulative percentage of drug Release

In vitro drug release profiles of prepared control release tablet of ibuprofen were shown in Table 14. The release of drug from the tablet exhibited a sustained pattern, in controlled manner over extended period of time. The release patterns of all the formulations were represented in Fig 5. Most of the formulations release drug in a constant manner except formulation F3 and F5. From the cumulative drug release data, the control release tablet formulation F2 was found to release the drug only 74 % even after 24 h, thus concluded to have sustained release of drug in constant manner for longer period of time when compared to other tablet formulations.

Stability studies:

Table 15. Stability data -parameters of optimized ibuprofen tablet formulation F2 for three months at 40°C /75% RH.

Sl. No	Parameters	Initial	1st month	2nd month	3rd month
1	Avg. weight (mg)	978	978	977	977
2	Hardness (kg/ cm^2)	3.5	3.5	3.5	3.5
3	Thickness (mm)	2.6	2.6	2.6	2.6
4	Friability (%)	0.025	0.025	0.025	0.025
5	Drug content (%)	99.5	99.45	99.25	99.07

Stability studies were carried out for optimized formulation (F2) for three months at 40°C /75% RH. The data of stability study is given in Table 15. No significant variation was found in hardness of the tablet, thickness, drug content and friability after three months in above storage condition, assuring optimized tablet will be stable during the storage condition.

8. CONCLUSION

Oral controlled drug delivery system is perhaps the relatively very advanced, newer area of research of its kind. This state-of-the-art formulation development offers several benefits like increased therapeutic efficacy, decreased side effects etc. Biocompatible and biodegradable xanthum gum, glyceryl behanate and stearic acid were experimented with ibuprofen which has served as a model drug for development of controlled release oral tablet.

Oral control tablet of ibuprofen with very good physical characteristics were developed. The method of preparation of tablet of ibuprofen was found to be simple and reproducible. The sustained release of ibuprofen from the development oral tablet will help to improve the therapeutic efficacy and patient compliance by reducing the dose and frequency of dosing of ibuprofen perhaps as *in vitro* dissolution study suggested only 74 % (F2) release of drug over 24 h period. This work shows that stearic acid loaded tablet of ibuprofen could be oral control drug delivery system for ibuprofen for prolonged release. Thus concluding control release tablet of ibuprofen could improve upon physicochemical and biological properties of ibuprofen.

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