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RESEARCH ARTICLE

Design, Development, and Evaluation of Nsaid Drug in Soft gel Dosage Form

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ABSTRACT

All the pharmaceutical products formulated for systemic delivery through the oral route of administration irrespective of the mode of delivery immediate sustained or controlled release and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics, and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

Keywords: Pharmacokinetics, Pharmacodynamics, Soft dosage form

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug through various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration and the belief that oral administration of the drug is well absorbed. All the pharmaceutical products formulated for systemic delivery through the oral route of administration irrespective of the mode of delivery immediate sustained or controlled release and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics, and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

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Soft gelatin capsules

Soft gelatin capsules are a single-unit solid dosage form, consisting of a liquid or semi-solid fill enveloped by a one-piece sealed elastic outer shell. The amount of drug or extract together with adjuvant is enclosed within a globular, oval or other shape of a soft shell. Soft gelatin in capsules offers the possibility of delivering a liquid in a solid oral dosage form. The softgel can contain the active ingredient in solution, suspension, or emulsion which will inherently lead to better absorption of the active ingredient as compared with delivery in a tablet or as a powder. Since the introduction of soft capsule making machine in the 1970s, formulations have continually become more popular with rapid development in recent years. Softgels ability to enhance bioavailability not only makes them the preferred dosage form for new chemical entities with poor oral bioavailability, but they can also be used for reformulation of existing drugs, with the purpose of lifecycle extension.[1-10]

Advantages

Increased the rate of absorption of drugs

This has been achieved using a drug solution matrix in a softgel formulation whereby absorption is significantly faster than from other solid oral dosage forms, such as compression tablets. While absorption of a poorly soluble drug from a tablet formulation is rate-limited by the need for disintegration into granules before drug dissolution into gastrointestinal fluid, the solution-softgel approach, the shell ruptures within minutes to release the drug solution, which leads to increase the rate of absorption of drugs.

Increased bioavailability of drugs

As well as increasing the rate of absorption, softgel has also been reported to improve the extent of absorption, this can be particularly effective for hydrophobic drugs with are latively high molecular weight. For example, protease inhibitor saquinavir as a softgel formulation provided around 3 times the bioavailability of saquinavir as measured by the area under the plasma time curve (AUC), compared to a hard-shell capsule formulation.

Decreased variability of plasmatic drugs

High variability in drug plasma levels is a common characteristic of drugs with low bioavailability. By dosing drug optimally in solution, the plasma level variability of such drugs has been significantly reduced.

For example, cyclic polypeptide drug cyclosporine was successfully improved by this approach by using a microemulsion pre-concentration in a softgel.

Patient compliance and consumer preference

A number of self-medicating consumer preference studies have been carried out in an attempt to gauge the relative perception of softgels compared to hard shell capsules and tablets. Using a softgel formulation, it may be possible to reduce the dose administered to therapeutic effectiveness, in this way it is possible reduce the capsule size, which will further improve patient compliance.

Safety for potent and cytotoxic drug

The mixing, granulation and compression/filling processes used in preparing tablets and hard-shell capsules have been noted to generate a significant quantity of air-borne powders. By preparing a solution or suspension of drug, where the active component is essentially protected from the environment by the liquid, such safety concerns and associated toxicities have been significantly reduced.

Dose uniformity of low dose drugs

Content uniformity can be achieved for formulations containing drug doses in the microgram region. Improved homogeneity has been achieved by dissolving the drug in a liquid and then encapsulating the liquid matrix in a softgel.

Product stability

Liquid filled softgel has beneficial to oxidative or hydrolytic degradable drugs. The liquid is prepared and encapsulated under a protective nitrogen atmosphere and the subsequently dried shell has very low oxygen permeability. The shell may be transparent and opaque. Opacity provides protection for photosensitive substances. Softgel capsules are also protected against UV radiation and light, which provides stability to the supplement and minimizes the formation of free radicals, and prevents specially rancidity. Soft gelatin capsules offer many advantages in comparison with other delivery systems. They are easy to swallow, have no taste (unless gelatin is intentionally flavored) odors and provide an elegant look.

Types of liquid fill formulations encapsulated

1. Solutions
    a. Hydrophilic vehicles (aqueous based fill formulation)
    b. Lipophilic vehicles (lipid-based fill formulation)
    c. Self-emulsifying oils (oil + non-ionic surfactant)
        i. Self-emulsifying drug delivery system
        ii. Self-micro-emulsifying drug delivery system

iii. Self-nano-emulsifying drug delivery system
2. Suspensions
3. Microemulsions and nanoemulsion.

Solutions

Aqueous based fill formulation (hydrophilic vehicles)

Hydrophilic vehicles for softgel fill formulations include polyethylene glycols (e.g., PEG 400, PEG 600), methoxy polyethylene glycols (Ex: MPEG 350, MPEG550), di-ethylene glycol mono ethyl ether, tetra hydro furfuryl alcohol polyethylene glycol, propylene carbonate, N-methyl-2-pyrrolidone (NMP), polyoxy ethylene-poly-oxy-propylene copolymers, propylene glycol, water, glycerin, and ethyl alcohol. The use of propylene glycol, glycerin, and water is restricted to less than 10% of the total fill formulation, as these vehicles can also act as plasticizers for the gelatin shell. Similarly, use of lower molecular weight polyethylene glycol (e.g., PEG 200 and PEG300) in the fill formulation is limited due to their ability to diffuse into the shell and their by act as a gelatin plasticizers. The extent of diffusion of a polyethylene glycol from the fill into shell decreases with increase in its molecular weight. The use of volatile components, such as ethyl alcohol in the fill formulation, is limited due to their ability to rapidly diffuse through the shell material.[11-20]

Solubility enhancers for hydrophilic vehicles

Using the solubility enhancers, can produce highly concentrated solutions for acidic, basic, and amphoteric compounds in hydrophilic vehicles suitable for filling softgels and also reduce the fill weight. The improvement of solubility of some compounds in polyethylene glycol by 40–400% using an ionizing agent (i.e., counter-ion, neutralizing agent). For example, the solubility of acidic compounds such as ibuprofen, naproxen, indomethacin, and acetaminophen in polyethylene glycol can be enhanced through partial ionization of these compounds with a hydroxide ion species (e.g., sodium hydroxide, potassium hydroxide, and ammonium hydroxide). Whereas the solubility of the basic compounds such as thioridazine, cimetidine, ranitidine, and nifedipine can be enhanced, through partial ionization with a hydronium ion species (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, and an organic acid). For amphoteric compounds, either hydroxide ion or hydronium ion sources may be used to enhance the solubility.

When using these neutralization techniques to obtain a highly concentrated solution of a compound, it is essential to keep the apparent pH of the final fill formulation at least between 2.5 and 7.5. At pH values below 2.5 gelatin gets hydrolyzed causing leakage of the softgel, whereas at pH values above 7.5 gelatin maybe either hydrolyzed or tanned (cross-linked) resulting in decreased solubility of the gelatin shell.

Alternately, the solubility of some compounds like acetaminophen, ibuprofen in hydrophilic vehicles can also be improved significantly using Povidone (polyvinyl pyrrolidone, PVP) as a solubility enhancer. The use of Povidone as a solubility enhancer results in a softgel fill formulation is very compatible with other softgel components. In addition, Povidone is available in a variety of molecular weights ranging from 2500 to 3,000,000, the viscosity of the fill formulation can be controlled through the selection of appropriate molecular weight and concentration of the polymer without adversely affecting the solubility of dissolved components. An advantage of using a higher amount of a lower molecular weight Povidone as a solubility enhancer is the reduction in the amount polyethylene glycol available in the fill formulation and also yields a fill formulation of a lower viscosity and thus improving the product manufacturer ability and dissolution characteristics.

Lipid-based fill formulations

Lipid-based fill formulation system was introduced as a working model in 2000. The main purpose of lipid formulation classification system is to enable *in vivo* studies to be interpreted more readily and subsequently to facilitate the identification of thermo stable appropriate formulations for specific drugs.

Self-microemulsifying drug delivery system (SMEDDS)

Self-microemulsifying drug delivery system (SMEDDS) is a very promising drug delivery system for oil-soluble drugs. It is a pre-mixing of drug, oil, surfactants, and co-surfactants and is able to form microemulsion *in vivo* or *in vitro* under gentle shaking or stirring spontaneously. SMEDDS is a very clear, isotropic, transparent, and thermodynamically stable system with a very small particle size (below 100 nm). A pseudo-ternary phase diagram of drug, oil, surfactant, co-surfactant, and water is used in formulating a suitable composition f SMEDDS. Usually, there are three types of phases in a pseudo-ternary phase diagram: Microemulsion (ME), liquid crystal (LC), and coarse emulsion (EM). ME region is the main region of interest in the formulation of SMEDDS. A large microemulsion region can offer more flexibility to find the optimal dosage composition. Microemulsions are identified with their clear and transparent appearance. Liquid crystal (LC) is a gel-like material that exhibits oil streaks under stirring condition. They also exhibit birefringence under crossed polarized microscope. Coarse emulsion (EM) is the traditional thermodynamically unstable emulsion; it appears as milky white. The droplet size of coarse emulsion can range from sub-micron to micron. The boundary lines between the two emulsion regions (ME and EM) are drawn out according to the emulsion appearance and droplet size.

Figure 1 is a typical ternary phase diagram. It represents a three-component system (oil, water, and surfactant). Ternary phase diagram can be read following the solid lines in the figure. For example, point A corresponds to a composition of 30% water phase, 60% surfactant phase, and 10% oil phase. The region to which point A belongs depends on the particle size and appearance of the sample. A titration technique is employed for the preparation of the ternary phase diagram (pseudo-ternary phase diagram). The titration procedure begins with zero loading of water. The dashed line (tie line) shown in the figure is followed with the addition of water. The titration procedure ends at a point of 100% water loading. The titration begins

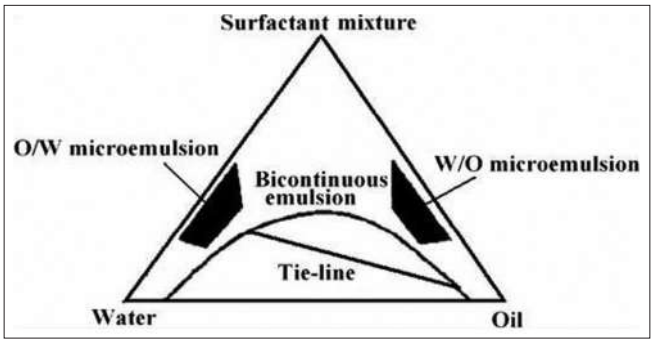

Figure 1: Tie lines of a pseudoternary phase diagram

by fixing two components and varying the third component SMEDDS can be described as oil (with drug) + surfactant + co-surfactant + water. Water comes from the aqueous phase present *in vivo*. No water is loaded in the drug preparation. The system with zero water loading is stored in capsules as reverse micelles before drug administration. The solubilization or the amount of drug present in reverse micelles is very important to evaluate the system. The drug solubilization ability of the system is one of the most important properties in the selection of the ingredients. Drugs are solubilized at the interface of microemulsion droplets or micelles. Reverse micelles have the higher drug capacity than the individual components. The reason for increasing capacity of drug solubilization is that the drug can distribute at the surface of the reverse micelle rather than occupy the core. The drug solubilization at reverse micelles surface is highly dependent on the physical properties of surfactant, co-surfactant, and drug, interaction between drug and surfactant and Hydrophilic-Lipophilic Balance Number (HLB) of surfactant. Different components can result in different solubilization capacity of the drug. However, drug solubilization reduces after oral administration due to aqueous phase dilution. During the phase inversion, water miscible components such as co-surfactant will move away from the surface and lead to decrease in drug solubilization.

Mechanism of enhancement of drug absorption in SMEDDS

The droplet size and polarity of oil droplets can influence the bioavailability of SMEDDS.

However, the polarity of oil droplets has a limited impact as the oil droplets are extremely small. A decrease in the particle size can enhance the drug absorption to a larger extent. The factors that influence the bioavailability of the SMEDDS were the first factor is surfactant. Surfactants can increase the drug permeability. They disrupt the lipid bi-layer on the epithelial cells membrane, a barrier to drug absorption and diffusion, to enhance the dissolution rate of the drugs. The second factor is the lipid. Oil phase can work not only as a carrier but also a shield to protect the attack and degradation from enzymes. Oil phase is necessary to deliver hydrophilic proteins to lymph systems. The hydrophilic proteins are incorporated in the water droplets of a w/o microemulsion. Hydrophilic proteins deliver in form of w/o microemulsion are called lipoproteins. Lipoproteins are highly lipophilic and can be transported to lymph system after absorption in small intestine. Drugs in lymph systems can reach systematic circulation directly without the first-pass effect. It has been proven that lipo proteins have a higher bioavailability than non-lipids. The third factor is called P-glycoprotein (P-gp) inhibition. P-glycoprotein is a type of combined protein existing in normal cells. It expels the drugs out of the cells as a self-biological defense and can reduce the drugs absorption. A recent study shows that drugs incorporated in SMEDDS can inhibit the activity of P-glycoprotein which results in an enhancement of oral absorption.

Suspension fills

Solids that are not sufficiently soluble in liquids or in combination of liquids are encapsulated as suspensions. Most organic and inorganic solids or compounds may be capsulated. Such materials must be 80 mesh or finer in particle size, due to certain close tolerances of the encapsulation equipment and for the maximum homogeneity of the suspension. Many compounds cannot be encapsulated, due to their solubility in water and thus their ability to affect the gelatin shell, unless they are minor constituents of a formula or are combined with a type of carrier (liquid or solid) that reduces their effect on the shell. Examples of such solids are strong acids (citric), strong alkalies (sodium salts of weak acids), salts of strong acids and bases (sodium chloride), and ammonium salts. Furthermore, any substance that is unstable in the presence of moisture (e.g., Aspirin) would not exhibit satisfactory chemical stability in soft gelatin capsules.

- Active medicament is dispersed in a suitable carrier.
- Suspensions can accommodate about 30% solids before viscosity and filling become a problem.
- Suspensions can be heated up to 35°C to decrease viscosity during the filling process.
- Suspended solids must be smaller than 80 mesh-mill or homogenizer before filling to prevent needles from clogging during filling.

The design of suspension type of formulation and a choice of suspending medium that will produce a smallest capsule size with maximum production capacity consist with maximum physical and ingredient stability and therapeutic efficacy. The formulation of suspensions for encapsulation follows the basic concepts of suspension technology. The formulation techniques depend on the drug substances, flow characteristics, physical or ingredient stability problems or biopharmaceutical properties desired. However, in the formulation of suspensions for soft gelatin encapsulation, certain basic information must be developed to minimize the capsule size.

Base adsorption of solids to be suspended in soft gelatin capsules

Base adsorption is expressed as the number of grams of liquid base required to produce a capsule a table mixture when mixed with 1 g of solid(s). The base adsorption of a solid is influenced by such factors such as the solids particle size and shape, its physical state (fibrous, amorphous, or crystalline), its density, moisture content, oleophilic, or hydrophilic nature. In the determination of base adsorption, the solid(s) must be completely wetted by the liquid base. For glycol and non-ionic type bases, the addition of a wetting agent is seldom required, but for vegetable oil bases, complete

wetting of the solid(s) is not achieved without an additive. Soy lecithin, at a concentration of 2–3% by weight of the oil, serves excellently for this purpose and being a natural product, is universally accepted for good drug use. Increasing the concentration above 3% appears to have no added advantage. A practice procedure for determining the base adsorption and for judging the adequate fluidity of a mixture is as follows: Weight a defined amount of the solid (40 g is convenient) into a 150 ml tared beaker. In a separate 150 ml tared beaker, place about 100 g of the solid base. Add small increments of the liquid base to the solid and using a spatula, stir the base into the solid after each addition until the solid is thoroughly wetted and uniformly coated with the base. This should produce a mixture that has a soft ointment like consistency. Continue to add liquid and stir until the mixture flows steadily from the spatula blade when held at a 45° angle above the mixture. The base adsorption is obtained by means of the following formula-Weight of the base/weight of the solid = Base Adsorption. The base adsorption is used to determine the "minim per gram" factor (M/g) of the solid(s). The minim per gram factor is the volume in the minims that is occupied by 1 g (S) of the solid plus the weight of the liquid base (BA) required to make a capsule a table mixture. The minim per gram factor is calculated by dividing the weight of the base plus the gram of solid base (BA+S) by the weight of the mixture (W) per cubic centimeter or minims (V). A convenient formula is:

$$(BA+S)\times V/W = M/g$$

Thus, lower the base adsorption of the solid (s) and higher the density of the mixture, the smaller the capsule will be. This also indicates the importance of establishing specifications for the control of those physical properties of a solid mentioned previously that can effect its base adsorption. The final formulation of a suspension invariably requires a suspending agent to prevent the settling of the solids and to maintain homogeneity before, during and after encapsulation. The nature and the concentration of the suspending agent vary. In all instances, the suspending agent used is melted in a suitable portion of the liquid base, and the hot melt is added slowly, with stirring, into the bulk portion of the base, which has been pre-heated to 40°C before the addition of any solids. The solids are then added one by one with sufficient mixing between additions to ensure complete wetting. Incompatible solids are added as far apart as possible in the mixing to prevent interaction before complete wetting by the base.

Examples of suspension fills include drug suspended in the following carriers

1. Oily mixtures
   a. Soya bean oil with beeswax (4–10% w/w) and lecithin (2–4% w/w). The lecithin improves material flow, and imparts some lubrication during filling. Add enough beeswax to get a good suspension, but avoid creating a non-dispersible plug.
   b. Gelified oil (e.g., Geloil® SC), a ready to use system composed of soybean oil, a suspending agent and a wetting agent.
2. Polyethylene glycol

PEG 800–1000 for semi-solid fills

PEG 10,000–100,000 for solid fills

Or mixtures of above (heat up to 35°C to make fluid enough for filling) Optional ingredients that can be added in the suspension fill:

- Surfactant; sorbitan derivatives such as polysorbate 80 or lecithin.
- For hydrophobic drugs dissolved or dispersed in an oily matrix, a surfactant of HLB

10 will increase the dispersibility of the product in the aqueous fluids and also may improve bioavailability.

Microemulsions and nanoemulsions

Microemulsions are isotropic, thermodynamically stable systems containing a very high concentration of surfactants. Microemulsion is an excellent carrier of oil based drugs. It has a small particle size, high stability, larger interfacial area, and low interfacial tension and forms spontaneously. The main difference between microemulsions and nanoemulsions is that microemulsions are self-assembling nano-scale emulsions whereas nanoemulsions are nano-scale emulsions formed

under intense mechanical shear. Microemulsions are isotropic solutions of oil and water and are prepared using a high surfactant concentration of around 40% under gentle stirring or shaking. Microemulsions form spontaneously without mechanical shear. An extremely high concentration of surfactants ensures self-assembling with particle size at the nano-scale level. Bowcott and Schulman have proved that self-micro-emulsification can happen when the oil-water interfacial tension is zero.

The interfacial tension is given as:

$$\gamma_i = \gamma_{OW} - \pi$$

Where, γ_{OW} is the interfacial tension without the presence of surfactant. π is the spreading pressure of surfactants at the interface. A large amount of surfactant can result in a high value of π. Therefore, the interfacial tension will reach a negative value. when $\pi > \gamma_{OW}$. A negative interfacial tension results in negative free energy and as a consequence microemulsion possesses high stability. Coarse emulsions are formed when $\pi < \gamma_{OW}$. The droplets of coarse emulsion tend to coalesce as the interfacial tension is positive.

The preparation of nanoemulsion requires extreme shear to rupture large droplets into nano-scale droplets. The mechanical shear should be intensive enough to overcome the large interfacial tension. Unlike microemulsion, nanoemulsions are thermodynamically unstable systems as the interfacial tension between oil and water phase is high. In the pharmaceutical field, non-ionic surfactants are widely used as they are less irritative than ionic surfactants. When the surfactant concentration exceeds a certain value, aggregates of surfactant called micelle are formed. The critical concentration of surfactant where micelles are formed is called critical micelle concentration (CMC). In water, the hydrophilic heads of the surfactant molecules are surrounded by water molecules and the hydrophilic tails of the surfactant molecules are gathered up in the inner portion of the micelles. In oil, the hydrophilic heads of the surfactant molecules are inside the micelles (reverse micelles) and the hydrophobic tails of the surfactant molecules extend away from the core of the micelles to the oil phase.

Microemulsions are three types:

1. W/O Microemulsion,
2. O/W Microemulsion,
3. Bi continuous microemulsion.

The characteristic properties of microemulsions are extremely low interfacial tension, large interfacial area and capability to solubilize two immiscible liquids, small particle size, and high thermodynamic stability.

Shell formulation

A softgel shell formulation typically consists of a film-forming material, such as gelatin, water dispersible or soluble plasticizer and water. The formulation may also contain other minor additives such as opacifiers, colorants, flavors, sweeteners, and preservatives. Softgels may also be coated with a variety of polymers for certain targeted enteral delivery applications.

Gelatin

The United States Pharmacopeia/National Formulary (USP/NF) defines gelatin as a product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue and bones of animals. Gelatin can be derived from many different sources of collagen with cattle bones, hides, pigskins and fish being the principle commercial sources. It contains a mixture of water soluble proteins (84–90%), mineral salts (1–2%), and water (8–15%). The protein fraction contains entirely of amino acids linked by amide bonds forming a linear polymer with a molecular weight ranging from 15,000 to 250,000 Da. Gelatin is derived from collagen by thermal de-naturating with the aid of either a dilute acid (type A gelatin) or a dilute alkali (type-B gelatin). Gelatin is amphoteric in nature with its isoelectric points ranging from 7.0 to 9.0 for type A gelatin and from 4.7 to 5.3 for type B gelatin, respectively. The alkaline hydrolysis causes a greater degree of deamidation of the asparagine and glutamine amino acids in collagen, resulting in the production of a larger number of free carboxylic acid groups in gelatin than that from acid hydrolysis. The greater degree of deamidation and the resulting

larger number of free carboxylic acid groups from the alkaline hydrolytic process accounts for the relatively lower isoelectric point of type B gelatin compared to that of type A gelatin. Type A gelatin usually has higher plasticity and elasticity than type B gelatin whereas, type B gelatin has higher gel strength.

Plasticizers

The high glass transition temperature of anhydrous gelatin (Tg > 100°C) prevents it from forming a flexible and acceptable film readily during the manufacturing of gelatin capsules. Water is an effective plasticizer for gelatin and reduces the Tg of gelatin proportionally to its water content. However, due to its volatile nature, water will be lost during the drying process resulting in a brittle and fragile shell. Thus, non-volatile plasticizers are included in the production of gelatin ribbons for softgels. The non-volatile plasticizers are hypothesized to substitute for water in the vicinity of the protein chains and reduce the protein-protein interaction with a consequent increase in the mobility of protein chains and a decrease in the Tg of gelatin. In addition, a plasticizer, due to its hygroscopic nature, may promote absorption of moisture by gelatin that also contributes to the reduction of forces between the adjacent polymer chains. In effect, considered the reduction in the Tg of gelatin. The reduction in the protein-protein interaction results in improving flexibility and handling of the shell material during its manufacturing and shelf life. Typically plasticizers used in the softgel shell formulation include glycerin, sorbitol, partially dehydrated sorbitol (a blend of D-sorbitol, 1,4-sorbitan, mannitol, and water, e.g., sorbitol special), maltitol, mannitol, propylene glycol. Selection of a plasticizer type and its concentration in the shell formulation is determined by gelatin type, composition of fill formulation and compatibility with the ingredients present in a fill formulation. Plasticizers are used typically at about 20–30% w/w of the total wet mass of a shell formulation. The addition of increasing amounts of a plasticizer alters the physical properties of a gelatin film resulting in an increase in its flexibility, elongation at break, water retention, water vapor permeability, decrease in its Tg, tensile strength, and elastic modulus.

Disease profile

The nonsteroidal anti-inflammatory drugs (NSAIDS) are widely used for the treatment of minor pain and for the management of edema and tissue damage resulting from inflammatory joint disease (arthritis) and also having the analgesic and antipyretic activity due to the inhibition of the prostaglandin synthesis by inhibiting the COX enzymes. Cyclo-oxygenase (COX) are responsible for the synthesis of prostaglandins and thromboxane, these causes the inflammation, pain, and rise in the temperature which causes the diseases like rheumatoid arthritis, osteo-arthritis, acute gouty arthritis, ankylosing spondylitis, dysmenorrhea due to excess prostaglandins, fever, general muscle pain and inflammation such as back pain, and headaches.

NSAIDS

NSAIDS have been commonly used in both human and veterinary medicine to reduce pain and inflammation in different arthritic and post-operative conditions due to their three major activities that are anti-inflammatory, antipyretic, and analgesic. The NSAIDS activity is mainly due to their ability to inhibit the activities of cyclo-oxygenases enzymes that mediate the production of prostaglandins from arachidonic acid, a dietary fatty acid.

Classification of NSAIDS

Depending on their chemical structures, NSAIDS are broadly divided into two major classes like, non-selective COX inhibitors and selective COX-2 inhibitors (Vane *et al*., 1998).

Classification based on chemical nature

1. Non-selective COX inhibitors
    a. Salicylic acid derivatives – for example, Aspirin, Sodium salicylate

b. Para-amino phenol derivatives – for example, Acetaminophen
c. Indole and indane acetic acids – for example, Indomethacin (Indocin), Sulindac (Clinoril)
d. Heteroaryl acetic acids – for example, Tometin (Tolectin), Diclofenac, Keterolac, Oxaprozin (Daypro)
e. Aryl propionic acids – for example, Ibuprofen (Motrin), Naproxen (Aleve, Anaprox), Flurbiprofen (Ansaid), Ketoprofen (Orudis), Fenoprofen, Oxaprofen, Carprofen (Rimadyl)
f. Anthranilic acids – for example, Mefenamic acid (Ponstel), Meclofenamic acid (Meclomen), Diclofenac (Voltaren)
g. Enolic acids (Oxicams) – for example, Piroxicam (Feldene), Tenoxicam, Isoxicam
h. Alkanones – for example, Nabumetone (Relafen™).

2. Semi selective COX-2 inhibitors
   E.g.: Meloxicam (Mobic), Etodolac (Lodine), Nabumatone (Relafen™), Nimesulide.
3. Selective COX-2 Inhibitors
   a. Diaryl substituted furanones – for example, Rofecoxib (Vioxx™).
   b. Diaryl substituted pyrazoles – for example, Celecoxib (Celebrex™)
   c. Diaryl substituted oxazole – for example, Valdecoxib (Bextra™).

Classification based on mode of inhibition of COX

Class I: Simple, competitive reversible inhibition that competes with arachidonic acid for binding to the COX site.
For example, Ibuprofen, piroxicam, sulindac, meclofenamic acid.
Class II: Competitive, time-dependent reversible inhibitors that bind to the COX active site in the first phase to form reversible enzyme inhibitor complex.
For example, Flurbiprofen, diclofenac.
Class III: Competitive, time dependent, irreversible inhibitors that form an enzyme inhibitor complex.
For example, Aspirin.

Mechanism of action

The major mechanism by which the NSAIDs elicit their therapeutic effects (antipyretic, analgesic, and anti-inflammatory activity) is inhibition of prostaglandin (PG) synthesis. Specifically NSAIDs competitively inhibit cyclo-oxygenases (COX), the enzyme that catalyzes the synthesis of cyclic endoperoxides from arachidonic acid to form prostaglandins. Two COX isoenzymes, for example, COX-1 and COX-2, COX-1 is synthesized continuously and is present in all tissues and cell types, mostly in platelets, endothelial cells, the GI tract, renal microvasculature, glomerulus, and collecting ducts. COX-1 has been proposed to generate prostaglandins that maintain organ function, protect the integrity of the gastric mucosa, and generate platelet-derived thromboxane responsible for platelet aggregation and vasoconstriction. Whereas, COX-2 is an inducible iso enzyme, although there is some constitutive expression in the kidney, brain, bone, female reproductive system, neoplasias, and GI tract COX-2 is induced during the inflammatory response and produces prostaglandins that mediate pain and inflammation.
All the NSAIDS produces anti-inflammatory effects by inhibiting cyclo-oxygenase enzymes which catalyses formation of prostaglandins, thromboxane from arachidonic acid. Exception to this is salicylic acid and acetaminophen on which inhibits COX enzymes irreversibly for entire cell life and centrally, respectively.

MATERIALS AND METHODOLOGY

Drug profile

NSAID drug

- Physicochemical properties

Description: The NSAID drug is a white to creamy white, crystalline powder.
Category: Nonsteroidal anti-inflammatory drug.
Structural Formula:
IUPAC Name: Sodium; (2S)-2-(6-methoxy naphthalen-2-yl) propanoate
Chemical Formula: $C_{14}H1_3NaO_3$
Molecular Weight: 252.24 g/mole.

Melting Point: Melting point of about 255°C with decomposition.
Solubility: It is insoluble in water and sparingly soluble acetonitrile, soluble in chloroform, methanol.

Mechanism of action

NSAID drug is a nonsteroidal anti-inflammatory drug (NSAIDs), which acts as an analgesic, anti-pyretic and anti-inflammatory medication. NSAID drug works at both the site of pain and centrally. The principle mechanism of action relies on the inhibition of prostaglandin synthesis. Prostaglandins are naturally occurring fatty acids derivate that is widely distributed in the tissues and are involved in the production of pain, fever, and inflammation. NSAIDs inhibit prostaglandin synthesis through inhibition of the cyclo-oxygenase enzymes. The anti-inflammatory and analgesic activity is based on concept that prostaglandins sensitize the tissues to pain and inflammation producing.
Mediators and anti-pyretic activity is assumed to be due to inhibition of prostaglandin synthesis in the hypothalamus induced by infectious states such as common cold.

Pharmacodynamics

NSAID drug is a member of arylacetic acid group of NSAIDs. The systemic bioavailability is about 95% in fasting subjects given in dose by mouth. NSAID drug is more than 99% bound to plasma protein and has a terminal elimination half-life of about 12–17 h. The renal elimination of drug is >95% of an oral dose.
Route of administration: Oral (220 mg)
Half-life: 12–17 h
Volume of distribution: 0.16 L/kg
Peak time (tmax): 2 h
PKa: 4.15
Log P: 3.18.

Pharmacokinetics

NSAID drug is an nonsteroidal anti-inflammatory agent which inhibits prostaglandin synthesis through inhibition of the cyclo-oxygenase enzymes.

Absorption

NSAID drug is promptly dissolves in the gastric juice to sodium and fine particles of naproxen. NSAID drug is rapidly and completely absorbed from the gastrointestinal tract. The systemic bioavailability is about 95%. The peak plasma level (C max) of 35 μg/ml is reached approximately 2 h after administration of dose.

Distribution

The volume of distribution of naproxen is small, about 0.16 L/kg. More than 99% of the circulating naproxen is albumin bound.

Metabolism

Naproxen is either metabolized by cytochrome P450 2C9, cytochrome P450 2C8, and cytochrome P450 1A2 enzymes to 6-0-desmethyl naproxen (6-DMN) and conjugated to glucuronides (UDP-glucuronosyltransferase 1-1, UDPglucuronosyltransferase 2B7) or left unmetabolized. Naproxen and its metabolites do not induce metabolizing enzymes.

Elimination

Naproxen and its metabolites are primarily excreted via the kidneys (>95%). The elimination half-life naproxen is about 12–17 h.

Preparations

Soft gelatin capsules of 220 mg are light green colored, 14 minims oblong shaped capsules.
Storage: Store between 20° and 25°C (°F).

Drug interactions

NSAID drug increases the therapeutic concentration of cyclosporine, which could induce nephrotoxicity. Also increases the concentration of lithium, methotrexate, and in these cases patients should be monitored. With this NSAID drug other NSAIDS should be avoided because of risk of

gastro-intestinal bleeding. In case of drugs such as anticoagulants, glucocorticoids, diuretics, antihypertensive drugs including ACE inhibitors, β-blockers, and patients should be monitored because of risk of gastro-intestinal bleeding, nephropathy.

Contraindications

NSAID drug is contraindicated in patients with a history of asthma, urticaria, or allergic type reactions after taking acetylsalicylic acid or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. NSAID drug is contraindicated in patients with active peptic ulcers, a history of recurrent ulceration or active gastrointestinal bleeding, with inflammatory bowel disease, with severe liver impairment or active liver disease, with severe renal impairment, in women in their third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and prolonged parturition.

Side effects

Common side effects (>1% incidence) may include abdominal pain, diarrhea, indigestion, and a general feeling of weakness. Rare side effects include joint pain, memory loss, and muscle cramps. Cholestatichepatitis, hepatic cirrhosis, rhabdomyolysis (destruction of muscles and blockade of renal system), and myositis have been reported in patients receiving the drug chronically serious allergic reactions to NSAID drug are rare. If the following signs of a serious allergic reaction occur seek medical attention immediately: Rash, itching/swelling, dizziness, difficulty swallowing/ breathing.

Uses

The primary uses of NSAID drugs are for the treatment of pain and reduction of fever. It also relieves arthritis pain, daily pain, and stiffness of arthritis, arthritis pain at rest and passive motion. It also relieves the night pain associated with arthritis, pain of inflammation, joint and body pain, muscular ache, pain of muscle sprains and strains, backache, headache, migraine pain, pain of menstrual cramps (dysmenorrhea), pain of minor surgery, toothache, pain of dental extractions, minor aches, and pain associated with the common cold.

Excipients

Olyethylene glycol

- Synonyms
  Carbowax, Carbowax sentry, Lipoxol, Lutrol E, Macrogola, PEG, Polyoxyethylene glycol, Pluriol E.
- Chemical name: α-Hydro-ω-hydroxypoly (oxy-1,2-ethanediyl)
- Molecular Formula: $HOCH_2$ (CH_2OCH_2) mCH_2OH where *m* represents the average number of oxyethylene groups.
- Structure
- Molecular weight: 190–9000 g/mole.
- Functional category: Ointment base, Plasticizer, solvent, suppository base, tablet, and capsule lubricant.
- Description:
  - Polyethylene glycol Grades 200–600 are liquids, grades 1000 and above are solids at ambient temperature.
  - Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow colored, viscous liquids. They have a slight but characteristic odor and bitter, slightly burning taste. PEG can occur as solid at ambient temperature.
  - Solid grades (PEG>1000) are white or off white in color, and range in consistency from pastes to waxy flakes. They have faint, sweet odor. Grades of PEG 6000 and above are available as free flowing milled powders.
- Typical properties
- Solubility
  - All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary).
  - Aqueous solutions of higher molecular weight grades may form gels.

- Liquid polyethylene glycols are soluble in acetone, alcohol, benzene, glycerine, and glycols.
- Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), methanol, they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils and mineral oils.

- Incompatibilities
  - The two terminal hydroxyl groups present in the polyethylene glycols are mainly responsible for its chemical reactivity, which can be either esterified or etherified.
  - All grades of polyethylene glycols exhibit some oxidizing activity due to the presence of peroxide impurities and secondary products formed by auto-oxidation.
  - The antibacterial activity of certain antibiotics such as penicillin and bacitracin is reduced in polyethylene glycol bases.
  - The preservative efficacy of the parabens is impaired due to binding with polyethylene glycols.
- Applications in pharmaceutical formulation or technology
  - Polyethylene glycols (PEGs) are used in a wide variety of pharmaceutical formulations such a parenterals, topical, ophthalmic, oral, and rectal preparations.
  - Polyethylene glycols are stable, hydrophilic substances, and non-irritant to skin. They do not readily penetrate the skin, although they are water soluble and easily removed from skin by washing, so useful as ointment base and suppository base. Solid grades are generally used in topical ointments and consistency was adjusted by using liquid grades of polyethylene glycol.
  - Liquid polyethylene glycols are used as water miscible solvents for contents of soft gelatin capsules.
  - Polyethylene glycol 300 and PEG 400 in the concentration up to 30% v/v are used as a vehicle for parenteral dosage forms.
  - When used in conjugation with other emulsifiers, PEG act as a emulsion stabilizers.
- Stability and storage conditions
  - PEGs are chemically stable in air and in solution, although grades with molecular less than 2000 are hygroscopic. PEGs do not support microbial growth, and they do not become rancid.
  - PEGs and aqueous PEG solutions can be sterilized by autoclaving, filtration, or gamma irradiation.
  - Oxidation may occur if PEGs are exposed for longer periods to temperature exceeding 500°C. PEGs should be stored in well closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for storage of liquid grades.

Povidone

- Synonyms
  - E1201, kollidon, plasdone, poly[1-(2-oxo-1-pyrrolidinyl)ethylene], povipharm, polyvidone, polyvinylpyrrolidone, povidonum, vinyl-2-pyrrolidinone polymer.
- Non-proprietary names
  - USP: Povidone
  - PhEur: Povidone
  - BP: Povidone
  - JP: Povidone.
- Empirical Formula: $(C_6H_9NO)n$, where *n* represents the average number
- Molecular weight: 2500–30,00,000 g/mole.
- Structure:Description:
  - Povidone occurs as a fine, white to creamy-white colored, odorless, hygroscopic powder.
- Functional categories
  - Disintegrant, dissolution enhancer, suspending agent, and tablet binder.
- Stability and storage conditions
  - Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C.
  - Povidone can be stored under ordinary conditions without undergoing decomposition. Since the powder is

hygroscopic, it should be stored in air tight container in cool, dry place.

- **Typical properties**
- Applications in pharmaceutical formulation or technology
  - In tableting, povidone solutions are used as binders in wet granulation process.
  - Povidone is used as a solubilize in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid dosage forms.
  - Povidone solutions also used as coating agents or binders.
  - Povidone is used as suspending, stabilizing or viscosity-increasing agent in topical and oral suspensions and solutions.
- Incompatibilities
  - Povidone is compatible in solution with a wide range of inorganic salts, natural, and synthetic resins and other chemicals.
  - It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbitol, tannins, and others.
  - The efficacy of some preservatives, for example, thimerosal may be adversely affected by formation of complexes with povidone.

Propylene glycol

- **Synonyms**
  - 1,2-Dihydroxypropane, E1520, 2-hydroxypropanol, methyl ethylene glycol, methyl glycol, propane-1,2-diol, propylenglycolum.
- Empirical Formula: $C_3H_8O_2$
- Structure:
- Molecular weight: 76.09 g/mole.
- Description:
  - Propylene glycol is clear, colorless, viscous, practically odorless liquid, with a sweet, slightly acrid taste resembling like glycerin.
- Functional categories
  - Antimicrobial preservative, disinfectant, plasticizer, stabilizing agent, water miscible cosolvent, humectant, and solvent.
- Stability and storage conditions
  - At cool temperatures, propylene glycol is stable in a well closed container, but at high temperatures, in the open, it tends to oxidize giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water.
- Applications
  - Propylene glycol widely used as a solvent, extractant and preservative in a variety of parenteral and non-parenteral pharmaceutical formulations.
  - It can dissolve a wide variety of materials such as corticosteroids, phenols, sulfa drugs barbiturates, vitamins (A and D), alkaloids, and local anesthetics.
  - Propylene glycol is commonly used as a plasticizer in aqueous film coating formulations.
  - Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicle for flavors in preference to ethanol, since it lacks of volatility provides a more uniform flavor.
- Typical properties

Lactic acid

- Onproprietary Names:
  - BP: Lactic acid
  - JP: Lactic acid
  - USP: Lactic acid
  - PhEur: Lactic acid
- Synonyms:
  - Acidumlacticum, E270, Eco-Lac, 2-hydroxypropanoic acid, α-hydroxypropionic acid, DL-lactic acid, Lexalt L, milk acid, Patlac LA, Purac 88 PH, racemic lactic acid.
- Chemical Name: 2-hydroxypropionic acid,
  - (R) – (-) -2-hydroxypropionic acid, (S) – (+) -2-hydroxypropionic acid, (RS) – (±) -2-hydroxypropionic acid.
- Empirical Formula: $C_3H_6O_3$
- Structure:

- Molecular weight: 90.08 g/mole.
- Description:
  - Lactic acid is a practically odorless, colorless or slightly yellow colored, viscous, hygroscopic, nonvolatile liquid.
- Functional categories: Acidifying agent, acidulant.
- Incompatability:
  - Incompatible with oxidizing agents, albumin. Reacts with nitric acid and hydrofluoric acid.
- Typical properties:
- Stability and storage conditions:
  - Lactic acid is hygroscopic in nature and will form condensation products such as poly lactic acid on contact with water. Lactic acid should be stored in a well closed container in a cool, dry place.
- Applications:
  - Lactic acid is used in beverages, foods, cosmetics, and pharmaceuticals as an acidifying agent and acidulant.
  - In topical formulations it is used for its softening and conditioning effect on the skin.
  - Lactic acid also used in the production of biodegradable polymers and microspheres, such as poly (D-lactic acid) used in drug delivery systems.
  - Lactic acid is used as food preservative.
  - Lactic acid is used in injections, in the form of lactate, as a source of bicarbonate for the treatment of metabolic acidosis, as a spermicidal agent in pessaries for treatment of leucorrhea.

Gelatin

- Nonproprietary Names:
  - BP: Gelatin
  - JP: Gelatin
  - USP: Gelatin
  - PhEur: Gelatin
- Synonyms:
  - Byco; Cryogel; E441; gelatin; gelatin; instagel; kolatin; solugel; vitagel.
- Empirical formula and molecular weight:
  - Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type a gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen obtained from cattle and pig bone, cattle skin (hide), pigskin, and fish skin. The protein fraction consists almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 20,000 to 200,000.
- Structure:
- Description:
  - Gelatin occurs as a light-amber to faintly yellow-colored, vitreous, and brittle solid. It is practically odorless and tasteless and is available as translucent sheets, flakes and granules or as a coarse powder.
- Functional categories:
  - Coating agent, film-forming agent, gelling agent, suspending agent, tablet binder, and viscosity increasing agent.
- Typical properties:
- Solubility
  - Practically insoluble in acetone, chloroform, ethanol (95%), ether, and methanol.
  - Soluble in glycerin, acids and alkalis, although strong acids or alkalis cause precipitation.
  - In water, gelatin swells and softens, gradually absorbing between 5 and 10 times its own weight of water.
  - Gelatin is soluble in water above 40°C, forming a colloidal solution, which gels on cooling to 35–40°C. This gel-sol system is thixotropic and heat reversible the melting temperature being slightly higher than the setting point; the melting point can be varied by the addition of glycerin.
- Viscosity (dynamic)
- Stability and storage conditions
  - Dry gelatin is stable in air. Aqueous gelatin solutions are also stable for long periods if stored under cool conditions but they are subject to bacterial degradation. Gelatin may be sterilized by dry heat.
  - The bulk material of gelatin should be stored in an airtight container in a cool, well ventilated, and dry place.

- Applications
  - Gelatin is widely used in a variety of pharmaceutical formulations, including its use as a biodegradable matrix material in an implantable delivery system, although it is most frequently used to form hard and soft gelatin capsules.
  - Soft gelatin capsules also include for rectal and vaginal administration.
  - Hard gelatin capsules can be filled with solid (powder, granules, pellets, tablets, and mixtures thereof), semisolid, and liquid filings.
  - Soft gelatin capsules can be filled with liquids (solutions, suspensions, emulsions, self-microemulsifying formulations), solids, and semi-solids preparations.
  - Gelatin is soluble in warm water (>30°C), and a gelatin capsule will initially swell and finally dissolve in gastric fluid to release its contents rapidly.
- Incompatibility
  - Gelatin is an amphoteric material and will react with both acids and bases. It may be hydrolyzed by most proteolytic systems to yield its amino acid components.
  - Gelatin will react with aldehydes and aldehydic sugars, anionic and cationic polymers, electrolytes, metal ions, plasticizers, preservatives, strong oxidizers, and surfactants. It is precipitated by alcohols, chloroform, ether, mercury salts, and tannic acid.

Glycerin

- Nonproprietary Names:
  - BP: Glycerol
  - JP: Concentrated glycerin
  - phEur: Glycerol
  - USP: Glycerin
- Synonyms
  - Croderol; E422; glycerol; glycerine; glycerolum; Glycon G-100; Kemstrene; Optim; Pricerine; 1,2,3-propanetriol; trihydroxypropane glycerol.
- Empirical formula: $C_3H_8O_3$
- Chemical name: Propane-1,2,3-triol
- Structure:
- Molecular weight: 92.09 g/mole.
- Description:
  - Glycerin is a clear, colorless, odorless, viscous, and hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose.
- Functional categories
  - Antimicrobial preservative, cosolvent, emollient, humectants, plasticizer, solvent, sweetening agent, and tonicity agent.
- Solubility
  - Slightly soluble in acetone, practically insoluble in benzene, chloroform and oils, soluble in ethanol (95%), methanol, soluble in water.
- Typical properties
- Stability and storage conditions

Glycerin is hygroscopic. Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions, but it decomposes on heating with the evolution of toxic acrolein. Mixtures of glycerin with water, ethanol (95%), and propylene glycol are chemically stable. Glycerin may crystallize if stored at low temperatures, the crystals do not melt until warmed to 20°C. Glycerin should be stored in an airtight container, in a cool, dry place.

- Applications
  - Glycerin is used in a wide variety of pharmaceutical formulations including oral, otic, ophthalmic, topical, and parenteral preparations.
  - In topical and cosmetic preparations, glycerin is used primarily for its humectants and emollient properties.
  - Glycerin is used as a solvent or co-solvent in creams and emulsions.
  - Glycerin is additionally used in aqueous and non-aqueous gels and also as an additive in patch applications.
  - In parenteral formulations, glycerin is used mainly as a solvent and co-solvent.
- Incompatibilities
  - Glycerin may explode if mixed with strong oxidizing agents such as chromium trioxide, potassium chlorate, or potassium permanganate.

- In dilute solutions, the reaction proceeds at a slower rate with several oxidation products being formed.
- Black discoloration of glycerin occurs in presence of light, or on contact with zinc oxide or basic bismuth nitrate.

Sorbitol special

- Non-proprietary names:
  - USP: Sorbitol-sorbitan solution
  - EP: Dehydrated liquid sorbitol
- Description: Sorbitol special occurs as an odorless, clear colorless viscous liquid.
- Viscosity (dynamic): 280 cP at 25°C
- Boiling Point: >100°C
- Functional category: Humectants, plasticizer, stabilizing agent, sweetening agent, and capsule diluent.
- Chemical composition:
- Applications
  - Sorbitol special decreases the glass transition temperature of gelatin without inhibiting formation of linkages that stabilize the three-dimensional gel network structure.
  - Sorbitol special inhibits migration of plasticizer into aqueous based PEG fill and also inhibits the blooming, which is white discoloration on surface of the capsule.
  - Sorbitol special MDF 85 is used as a plasticizer in soft gel preparation, in where the active pharmaceutical ingredient is incompatible with glycerin.
  - Sorbitol special A-810 is also a special grade of which containing 56% sorbitol special and 44% glycerin is used in the special cases of formulation.

Experimental studies

Pre-formulation studies

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and combined with excipients [Figures 2-11]. It is the first step in the rationale development of the dosage forms. Pre-formulation studies yield necessary knowledge to develop suitable formulations. It gives information about the nature of the drug substance. Hence, the following pre-formulation studies were performed for the obtained sample of drug.

- Organoleptic evaluation
- Particle size distribution
- Drug-excipient compatibility study
- Solubility Studies
- UV method development for estimation of drug

The methods are described below,

- Organoleptic evaluation

The color and odor of the NSAID drug were evaluated and tabulated using descriptive terminology.

- Particle size determination: dry sieving method

An accurately weighed quantity of test specimen was placed on the top (coarsest) sieve, and lid was replaced. The nest of sieves was agitated for 5 min. Then, each sieve was carefully removed from the nest without loss of material. Each sieve was reweighed, and the weight of material on each sieve was determined. The weight of material in the collecting pan was also determined in a similar manner. The nest of sieves were reassembled and agitated for 5 min. Each sieve was removed and weighed the quantity. On completion of the analysis, the weights of material were reconciled. Total losses must not exceed 5% of the weight of the original test specimen.

- Determination of melting point

Capillary melting point or a melting–point apparatus is most often used for the determination of the melting point of a solid. A few crystals of the drug was placed in a thin walled capillary tube 10–15 cm long about 1 mm inside diameter and closed at end. The capillary, which contains the sample, and a thermometer were then suspended so they can be heated slowly and evenly. The temperature range at which the sample was melted was taken as the melting point.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

- Physical observation

Physical mixtures of drug and excipients were prepared by grinding specific ratios of drug and excipients in a mortar. Sample of 3–4 g was taken and loaded in a glass vial, covered with rubber stopper, sealed with aluminum cap, and labeled properly. Samples were observed and color was recorded for initial evaluation and loaded into stability chamber at temperature of 40°C and 75% relative humidity, 25°C and 60% relative humidity for 4 weeks compatibility study. Samples were withdrawn at 1 week interval for 4 weeks and observed for any color and odor change. At the end of 4th week samples were removed, observations were recorded and further analysis was carried out using DSC and FTIR.

- Fourier transform infrared spectroscopy (FT-IR)

Principle

FT-IR stands for Fourier Transform Infrared, the preferred method of infrared spectroscopy. In infrared spectroscopy, IR radiation is passed through a sample. Some of the infrared radiation is absorbed by the sample and some of it is passed transmitted. The resulting spectrum represents the molecular absorption and transmission, creating a Molecular finger print of the sample. Like a finger print no two unique molecular structures produce the same infrared spectrum. This makes infrared spectroscopy useful for several types of analysis. FT-IR samples were mixed with KBr in the ratio 1:100 and pressed into pellets. Pellets were analyzed at wavelength range 4000–450 cm^{-1} with resolution of as 4 cm^{-1}.

Sample preparation

- Completely dried potassium bromide was transferred into a mortar. About 2% of pure drug or with excipients was weighed in digital balance, mixed, and grinded to a fine powder. Two stainless steel disks were taken out of the desiccators. A piece of the pre-cut cardboard (in the tin can next to the oven) on top of one disk was placed and cut out hole was filled with the finely ground mixture.
- The second stainless steel disk was kept on top and transfers the sandwich onto the pistil in the hydraulic press. With a pumping movement, hydraulic pump handle moved downward. The pistil will start to move upward until it reaches the top of the pump chamber.
- The pump handle moved upward and continued pumping until the pressure reaches 20,000 prf. Rest for a few seconds and with the small lever on the left side, the pressure was released. Removing of the disks and pulling apart. Obtained film was homogenous and transparent in appearance. Then inserted into the IR sample holder and attach with scotch tape and run the spectrum.

Solubility of API

Solubility of substances NSAID drug was determined in different solvents by shake flask method for 24 h at 37°C. Excess drug was added carefully using a spatula to 10 ml of the aqueous buffer in a conical flask, while stirring until a heterogeneous system was obtained. The solution containing excess solid was then capped, and stirred at 150 rpm at the room temperature for 24 h.

Analytical methods preparation of standard stock

100 mg of NSAID drug was taken and added to respective media in a 100 ml volumetric flask and volume was made up to 100 ml, resulting in a standard stock solution of 1000 mcg/ml.

Preparation of working stock

From the above prepared standard stock solution, 10 ml was taken and added to respective buffer media in a 100 ml volumetric flask and volume was made up to 100 ml then obtained 100 mcg/ml solutions. From the working stock solution dilutions were prepared using respective media.

Determination of absorption maxima

10 µg/ml solution was taken to determine absorption maxima. Initially, blank buffer solution

was kept and scanned in the region of 200–400 nm. Then, sample was kept for analysis and scanned in the same region. Absorption maxima was found to be 272 nm. Hence, all further analysis was carried out at 272 nm in 0.01N HCl (pH 2.01), 0.1N HCl (pH 1.05), pH 4.5 sodium acetate buffer, pH 7.5 phosphate buffer, and pH 6.8 phosphate buffer.

Standard curve of drug in 0.1 N hydrochloric acid

10 mg of drug was accurately weighed and dissolved in 10 ml methanol to prepare the stock solution. 10 ml sample was taken from the above solution and diluted to 100 ml of 0.1N hydrochloric acid to prepare the working standard. The aliquot amount of this solution was diluted with 0.1 N hydrochloric acid to get 10 μg/ml, 20 μg/ml, 30 μg/ml, 40 μg/ml, and 50 μg/ml of drug per ml of the final solution. Then, the absorbance was measured in UV Spectrophotometer at 272 nm against 0.1N hydrochloric acid as blank and the regression equation was computed.

Standard curve of drug in 0.01 N hydrochloric acid

10 mg of drug was accurately weighed and dissolved in 10 ml methanol to prepare the stock solution. 10 ml sample was taken from the above solution and diluted to 100 ml of 0.01N hydrochloric acid to prepare the working standard. The aliquot amount of this solution was diluted with 0.01N hydrochloric acid to get 10 μg/ml, 20 μg/ml, 30 μg/ml, 40 μg/ml, and 50 μg/ml of drug per ml of the final solution. Then, the absorbance was measured in UV Spectrophotometer at 272 nm against 0.01N hydrochloric acid as blank and the regression equation was computed.

Standard curve of drug in pH 6.8 phosphate buffer

10 mg of drug was accurately weighed and dissolved in 10 ml methanol to prepare the stock solution. 10 ml sample was taken from the above solution and diluted to 100 ml of pH 6.8 phosphate buffer to prepare the working standard. The aliquot amount of this solution was further diluted with pH 6.8 phosphate buffer to get 10 μg/ml, 20 μg/ml, 30 μg/ml, 40 μg/ml, and 50 μg/ml of drug per ml of the final solution. Then, the absorbance was measured in UV Spectrophotometer at 272 nm against pH 6.8 phosphate buffer as blank and the regression equation was computed.

Standard curve of drug in pH 7.5 phosphate buffer

10 mg of drug was accurately weighed and dissolved in 10 ml methanol to prepare the stock solution. 10 ml sample was taken from the above solution and diluted to 100 ml of pH 7.5 phosphate buffer to prepare the working standard. The aliquot amount of this solution was further diluted with pH 7.5 phosphate buffer to get 10 μg/ml, 20 μg/ml, 30 μg/ml, 40 μg/ml, and 50 μg/ml of drug per ml of the final solution. Then, the absorbance was measured in UV Spectrophotometer at 272 nm against pH 7.5 phosphate buffer as blank and the regression equation was computed.

Standard curve of drug in pH 4.5 acetate buffer

10 mg of drug was accurately weighed and dissolved in 10 ml methanol to prepare the stock solution. 10 ml sample was taken from the above solution and diluted to 100 ml of pH 4.5.

Acetate buffer is to prepare the working standard solution. The aliquot amount of this solution was diluted with pH 4.5 acetate buffer to get 10 μg/ml, 20 μg/ml, 30 μg/ml, 40 μg/ml, 50 μg/ml of drug per ml of the final solution. Then, the absorbance was measured in UV Spectrophotometer at 272nm against pH 4.5 acetate buffer as blank and the regression equation was computed.

Formulation development preparation of soft gelatin capsules of NSAID drug

NSAID drug soft gelatin capsules, each containing 220 mg of NSAID drug were prepared by encapsulation of liquid fill medicament into a gelatin shell.

- **Step-1: Preparation of medicament**
  - Collect calculated quantity of Polyethylene glycol and propylene glycol in medicament manufacturing tank by filter through #200 mesh nylon cloth.
  - Add and dissolve Povidone K in the medicament manufacturing tank with continuous mixing and heated up to 70–80°C. Add calculated quantity of lactic acid and water into medicament manufacturing tank with continuous mixing.
  - Add and dissolve calculated quantity of NSAID drug into the medicament manufacturing tank with continuous heating up to 85–90°C and mixing for 90–120 min. Allow the medicament to cool at room temperature below 30°C. Unload the medicament into medicament holding tank by pass through #200 mesh nylon cloth.
- **Step-2: Preparation of gelatin mass**
  - Transfer the Glycerin and Sorbitol special solution, purified water by filter through #200 mesh nylon cloth under stirring into the Gelatin melter by applying vaccum and maintain the temperature 80–85°C.
  - Transfer the Gelatin into the Gelatin melter by applying vaccum with continuous mixing at fast speed and continuous heating for 90–120 min or till it gets completely melted. Maintain the gelatin mass temperature 60–70°C.
  - Carry out the de-aeration by applying vacuum at 600–650 mm of Hg for 30–45 min and remove the extra amount of water and air bubbles entrapped inside the Gelatin mass.
  - Check and ensure the gelatin mass should not contain gelatin lumps and air bubbles.
  - Collect 15 mg of purified water in a SS vessel and dissolve FD&C Blue No. 1, add into gelatin melter with continuous mixing.
  - Rinse the SS vessel with 10 mg of purified water and add into gelatin melter with continuous mixing for 20–30 min. Unload the gelatin mass into pre heated gelatin holding tank temperature 55°C ± 5°C by pass through #40 mesh.
  - Note: keep gelatin holding tank aside for 4–6 h for maturation of gelatin mass.

Switch "OFF" the gelatin holding tank temperature, if not use for encapsulation. Switch "ON" the gelatin holding tank heater 6 h before starting the encapsulation process.

PRILIMINARY OPTIMIZATION TRAILS

- **Step-3: Encapsulation process**
  - Transfer the gelatin holding tank and medicament holding tank into encapsulation area.
  - Connect medicament transfer pump to hopper and hopper to medicament holding tank by using medicament transfer pipe.
  - Connect gelatin holding tank to spreader box with gelatin transfer pipe with temperature controlling insulated wire.
  - Maintain the following parameters:
  - Gelatin holding tank temperature: 60°C ± 5°C
  - Spreader box temperature: 55°C ± 5°C
  - Cool drum temperature: 9°C ± 5°C
  - Segment temperature: 40°C ± 5°C
  - Encapsulation machine RPM: 1.0–3.5
  - Die roll: 14 minim oblong
  - Fill the polyethylene glycol into the hopper and start the encapsulation machine and adjust the gelatin ribbon thickness and medicament weight.
  - Discard the polyethylene glycol from hopper and polyethylene glycol capsules.
  - Fill the medicament into hopper using medicament transfer pump and circulate the medicament for 10–15 min for clear the air bubbles.
  - Carry out the encapsulation, check and adjust the proper fill weight, ribbon thickness.
- **Step-4: Drying**

Semi drier/tumble drier

Place 2 numbers of Kimberly cloths in each tumble for wiping the extraneous oil present on the

capsules and replace with new cloth at every 60 min. After encapsulation, transfer the wet capsules into tumble drier and carry out the tumble drying process for 30 min. Collect the semi dried capsules on cleaned drying trays in a monolayer and stack these trays into the trolleys and transfer into drying area.

Drying area/tunnel dryer

Transfer the trolleys to the capsule drying area. Carry out the shuffling for every 6 h till completion of drying process, remove, and discard the medicament leaked capsules, de-shaped capsules. Observe and control the following parameters during drying.

Drying area condition

Temperature: 23°C ± 2°C
Humidity: Not more than 20% RH Duration: 48–72 h.

- **Step-5: Inspection**

Carry out the inspection for dried capsules and discard the rejected capsules such as De-shape, Leak, twin caps, air bubbles present in gelatin shell, Foreign particles on capsules surface, and sealing defected capsules.

- **Step-6: Polishing**

Transfer the inspected capsules to polishing area. Load the capsules into polishing pan. Carry out the polishing using oil absorbing clothes. Allow the capsules to revolve in polishing pan for NLT 30 min.

- **Step-7: Printing**

Transfer the good capsules into printing area and carry out the printing using capsule printing machine with text "NPX 220" with opacode black edible ink.

Formulation evaluation

Evaluation of parameters during encapsulation

- Weight variation test
  - During the encapsulation process the softgel capsules were tested for weight variation to adjust the fill weight and to obtain a uniform weight of capsules. Weight variation is done by checking the fill weight, shell weight, and gross weight.
  - Twenty softgel capsules were randomly selected from each formulation and their gross weight was calculated using digital balance. Individual weights of each capsule was weighed, then empty the contents of capsule and reweight the empty shell and calculated the fill weight and compared with the average weight.
- Gelatin shell thickness
  - The gelatin shell thickness was adjusted using the spreader box. The shell weight will vary according to the thickness of gelatin shell.

Evaluation of parameters after encapsulation for dried capsules

- Physical appearance
- Weight variation
- Hardness
- Dimensions
- pH of medicament
- *In vitro* drug release
- Drug content.

Physical appearance

The softgel capsules were inspected for color uniformity, smoothness, absence of disshaped, size, and other undesirable characteristics.

Weight variation test

Twenty softgel capsules were randomly selected from each formulation and their gross weight was calculated using digital balance. Individual weights of each capsule were weighed, then empty the contents of capsule and reweight the empty shell and calculated the fill weight and compared with the average weight.

Hardness

The hardness test is performed to measure the softgel capsule strength. Capsule should be hard

enough to withstand packing and shipping. Barries hardness tester was used for the determination of hardness of softgel capsules. The hardness of ten softgel capsules were noted and the average hardness was calculated. It is expressed in kp or N.

Dimensions

Dimensions were determined for 20 softgel capsules of each batch using a digital Vernier scale and the average length and width was determined in mm.

pH

The pH of the medicament in the softgel capsules were determined by emptying the fill medicament from the capsule shell. The pH of the medicament should be within the specified limits.

Assay (drug content)

The medicament fill from the softgel capsules were collected equivalent to 50 mg was taken and dissolved in pH 7.4 phosphate buffer and made up 100 ml in volumetric flask. Absorbance was measured at 272 nm with pH 7.4 phosphate buffer as blank and drug content was calculated.

Dissolution study

The dissolution test measures the rate of release of the drug from the dosage form *in vitro*, it is usually expressed as extent of dissolution (% drug content) occurring after a given time under specified conditions. For effective absorption of oral solid dosage form, simple disintegration of the dosage form is not adequate and the dissolution of the drug into the surrounding medium plays a vital role. Although dissolution is not a predictor of therapeutic efficacy, it can be looked upon a tool which can provide valuable information about biological availability of drug and batch to batch consistency. Dissolution is considered as one of the most important quality control tests performed for pharmaceutical dosage form.

Chemicals and reagents

a. Working standard
b. pH 7.4 sodium phosphate buffer.

Dissolution conditions

Medium: pH 7.4 sodium phosphate buffer
Volume: 900 mL
Temperature: 37°C ± 0.2°C
Apparatus: USP Type-2 (Paddle type)
Rpm: 75
Time interval l: 10, 15, 20, 30, 45, and 60 min.

Preparation of dissolution medium

8.5 ml of HCl was taken and to it water was added make up to 1 l, and it is passed through 0.45 µ membrane filter.

Procedure

The *in vitro* dissolution study was carried out in the USP dissolution test apparatus, type-2 (paddle). One softgel capsule was placed in each of the six dissolution flasks containing 900 mL of dissolution medium, previously maintained at 37° ± 0.2°C. After completion of each specified time interval, a portion of the solution was withdrawn from zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1 cm from vessel wall and filtered through 0.45 µm membrane filter. The samples were collected at specified time intervals and diluted to required volume with dissolution medium. The absorbance's of the standard and sample preparations were measured at 272 nm in 1 cm cells, with a suitable spectrophotometer using dissolution medium as blank. Finally, the percentage drug dissolved was calculated.

Study of release kinetics

The results of *in vitro* release profiles obtained for all the formulations were fitted into four models of data treatment as follows:

1. Cumulative percent drug released versus time (zero-order kinetic model).

2. Log Cumulative percent drug remained versus time (first-order).
3. Cumulative percent drug released versus square root of time (Higuchi's model).
4. Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).

Mechanism of drug release

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Q_t = K_{0t}$$

Rearrangement of equation yields:

$$Q_t = Q_0 + K_t$$

Where Q_t is the amount of drug dissolved in time *t,* Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$), and K0 is the zero-order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released versus time.

Application

This relationship can be used to describe the drug dissolution of several types of immediate release, modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low-soluble drugs in coated forms, osmotic systems, etc.

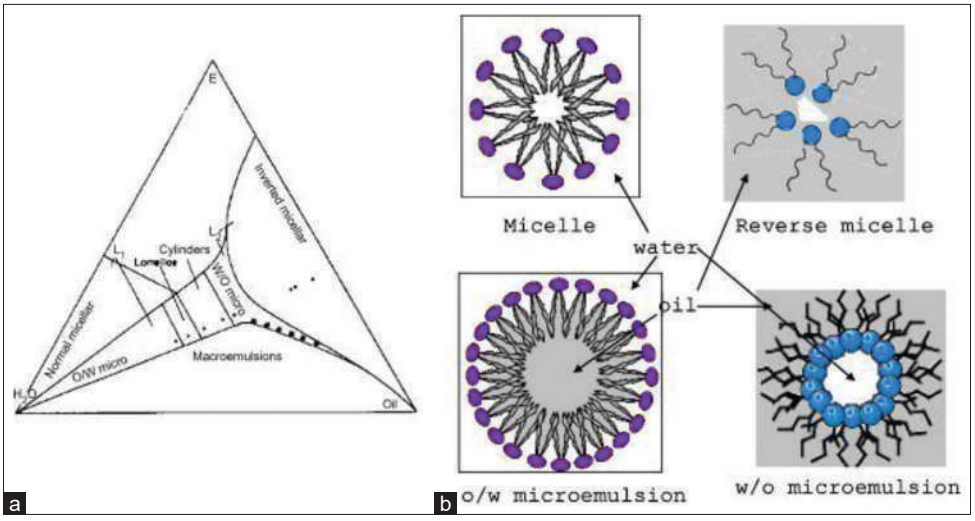

Figure 2: (a and b) Schematic representation of the dispersed phase structure of micelles, reverse micelles, O/W microemulsion and W/O microemulsion

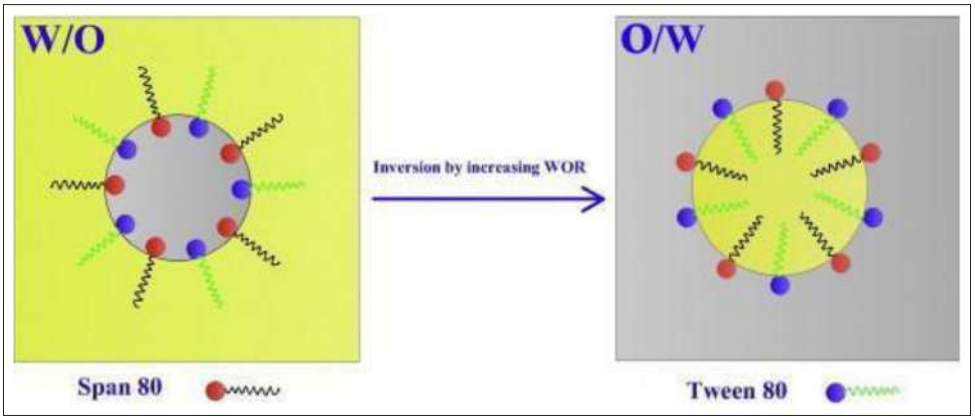

Figure 3: Schematic illustration of phase inversion (O/W microemulsion, bi continuous microemulsion, W/O microemulsion)

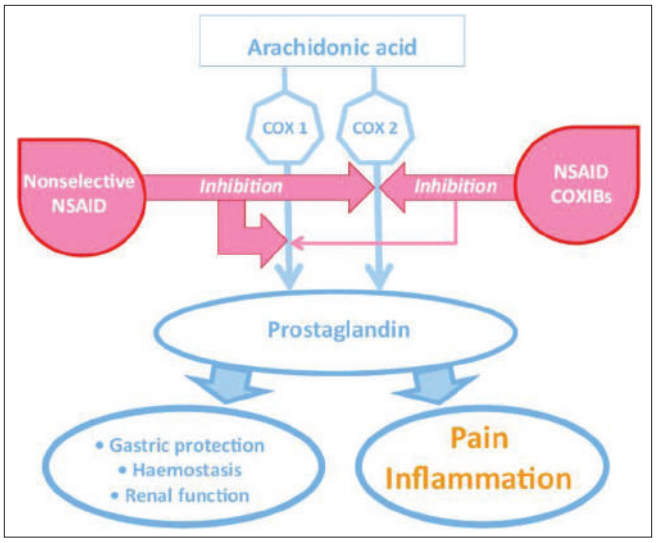

Figure 4: Flow chart for mechanism of NSAIDs

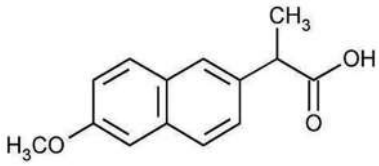

Figure 5A: Structural formula of NSAID drug

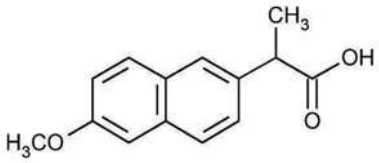

Figure 5B: Structural formula of NSAID drug

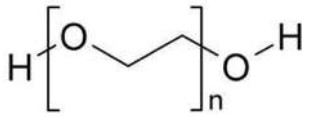

Figure 6: Structural formula of polyethylene glycol

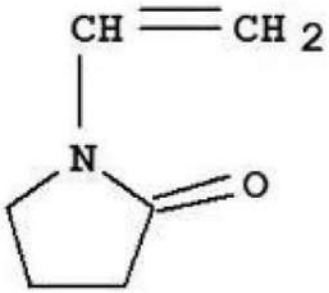

Figure 7: Structural formula of povidone

First-order model

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first-order kinetics can be expressed by the equation:

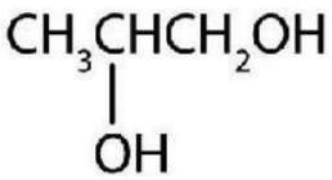

Figure 8: Structural formula of propylene glycol

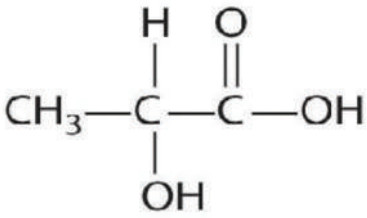

Figure 9: Structural formula of lactic acid

$$dC/dt = -KC$$

Where K is first-order rate constant expressed in units of time-1.

This equation can be expressed as:

$$\log C = \log C_0 - kt/2.303$$

Where C_0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining versus time which would yield a straight line with a slope of -k/2.303.

Application

This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing poorly water-soluble drugs.

Higuchi model

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Higuchi in 1961. Initially conceived for planar systems, it was then extended to different geometrics and porous systems. This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible); (iii) drug particles are much smaller than system

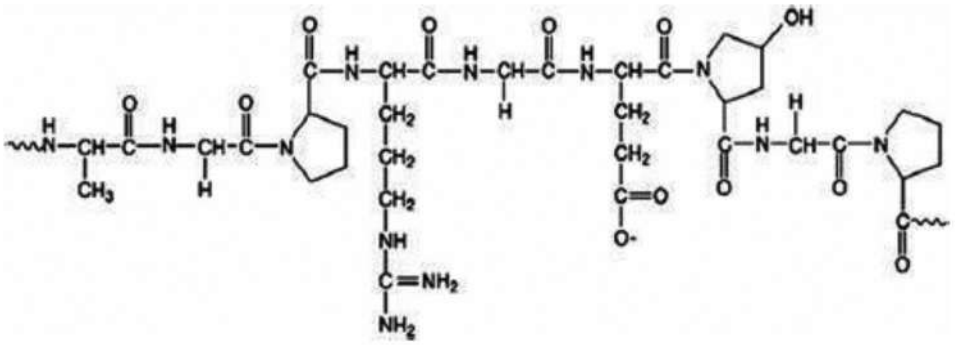

Figure 10: Structural formula of gelatin

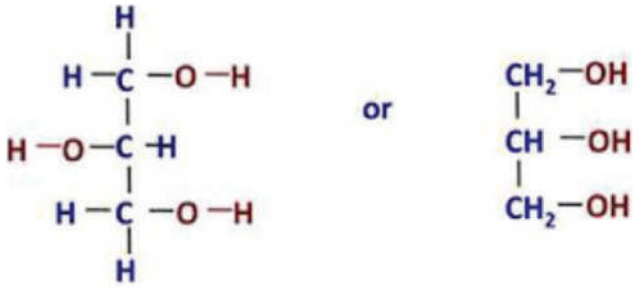

Figure 11: Structural formula of glycerin

thickness; (iv) matrix swelling and dissolution are negligible; (v) drug diffusivity is constant; and (vi) perfect sink conditions are always attained in the release environment.

Application

This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some trans dermal systems and matrix tablets with water soluble drugs [Figures 15-20].

Korsmeyer-Peppas model

Korsmeyer *et al*. (1983) derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, drug release data were fitted in Korsmeyer–Peppas model.

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release versus log time.

RESULTS AND DISCUSSION [Tables 1 and 2]

Results preformulation studies

- PI characterization
- Melting point determination
  - The melting point of the NSAID drug was determined by capillary tube method and it was found to be 255°C.
- Solubility studies of NSAID drug [Tables 4-19]

Fourier transform infrared spectroscopy (FT-IR)

FT-IR stands for Fourier Transform Infrared, the preferred method of infrared spectroscopy. In infrared spectroscopy, IR radiation is passed through a sample. Some of the infrared radiation is absorbed by the sample and some of it is passed through (transmitted). The resulting spectrum represents the molecular absorption and transmission, creating a molecular fingerprint of the sample. FT-IR samples were mixed with KBr in the ratio 1:100 and pressed into pellets. Pellets were analyzed at wavelength range 4000–450 cm^{-1} with resolution of as 4 cm^{-1}.[21-24]

FTIR spectrum of physical mixture of optimized formulations [Tables 23 and 26]

Determination of λ max For NSAID drug

10 mg of pure drug was taken and dissolved in pH 7.4 phosphate buffer and after suitable dilution [Tables 31-37], it was scanned from 200–400 nm against the blank solution to determine the absorption maxima for the model drug. The spectrum obtained and the λmax of NSAID drug were found to be 272 nm. Hence, all further investigations were carried out at the same wavelength.

Table 1: Typical properties of various grades of PEG polymer

Density	1.11–1.14 g/cm^3 at 25°C for liquid PEGs, 1.15–1.21 g/cm^3 at 25°C for solid PEGs.
Flash point	182°C for PEG 200, 213°C for PEG 300, 238°C for PEG 400, 250°C for PEG 600.
Freezing point	< −65°C PEG 200 sets to a glass, −15–−8°C for PEG 300, 4–8°C for PEG 400, 15°–25°C for PEG 600.
Melting point	44–48°C for PEG 1500, 44–48°C for PEG 1540, 45–50°C for PEG 2000, 48–54°C for PEG 3000, 50–58°C for PEG 4000, 55–63°C for PEG 6000, 60–63°C for PEG 8000, 60–63°C for PEG 20000.
Moisture content	Liquid polyethylene glycol is very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, for example, PEG 4000 and above are not hygroscopic.
Refractive index	n^{25}_D=1.459 for PEG 200 n^{25}_D=1.463 for PEG 300 n^{25}_D=1.465 for PEG 400 n^{25}_D=1.467 for PEG 600
Surface tension	44 mN/m (44 dynes/cm) for liquid polyethylene glycol, 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

Table 2: Various grades of PEG polymer grades and viscosity

PEG polymer grades	Average molecular weight (g/mole)	Nominal viscosity [mm^2/s (cSt)] at 250°C
PEG 200	190–210	39.9 cP
PEG 300	285–315	68.8 cP
PEG 400	380–420	90.0 cP
PEG 600	570–613	131 cP
PEG 1000	950–1050	19.5 cP
PEG 2000	1800–2200	47 cP
PEG 4000	3000–4800	180 cP

Table 3: Various properties of povidone

Acidity/ Alkalinity	pH=3.0–7.0 (5% w/v aqueous solution) pH=4.0–7.0 (5% w/v aqueous solution) for *Povipharm*K90
Density (bulk)	0.29–0.39 g/cm^3 for *Plasdone*
Density (tapped)	0.39–0.54 g/cm^3 for *Plasdone*
Density (true)	1.180 g/cm^3
Flowability	20 g/s for povidone K-15, 16 g/s for povidone K-29/32
Melting point	Softens at 1500°C
Moisture content	Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.
Particle size	*Kollidon* 25/30: 90% >50 μm, 50% >100 μm, 5% >200 μm,
Distribution	*Kollidon* 90: 90% >200 μm, 95% > 250 μm.
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 solution is limited only by the viscosity of the resulting solution, which is the function of K-value.
Viscosity (dynamic)	The viscosity of aqueous Povidone solutions depends on both the concentration and molecular weight of polymer employed.

Table 4: Different grades of povidone

K-value	Approximate molecular weight (g/mole)
12	2500
15	8000
17	10,000
25	30,000
30	50,000
60	400,000
9	1,000,000
120	3,000,000

Calibration curve of NSAID drug in pH 7.4

Evaluation of NSAID drug soft gelatin capsules

- In-process encapsulation parameters

In vitro drug release studies

The *in vitro* dissolution studies were performed using the USP-II (paddle) dissolution apparatus at 75 rpm. The dissolution medium consisted of 900 ml of pH 7.4 phosphate buffer maintained at the temperature of 37°±0.5°C. An aliquot 10 ml was withdrawn at specific time intervals and drug content was determined by UV-Visible spectrometer at 272 nm.

Similarity factor and dissimilarity factor calculation

- The similarity factor (f2) was defined by CDER, FDA, and EMEA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference release profiles."

Table 5: Various properties of propylene glycol

Auto ignition temperature	371°C
Boiling point	188°C
Density	1.038 g/cm^3 at 20°C
Flammability	Upper limit, 12.6% v/v in air; Lower limit, 2.6% v/v in air
Flash point	99°C (open cup)
Heat of combustion	1803.3 kJ/mol (431.0 kcal/mol)
Heat of vaporization	705.4 J/g (168.6 cal/g) at b.p
Melting point	59°C
Osmolarity	A 2.0% v/v aqueous solution is iso-osmotic with serum
Refractive index	n^{20}_{D}=1.4324
Specific rotation	$[\alpha]^{21}_{D}$ = −15.00 (neat) for (R)-form; $[\alpha]^{21}_{D}$ = +15.80 (neat) for (R)-form
Solubility	Miscible with acetone, chloroform, ethanol (95%), glycerin, water; Soluble in 1 in 6 parts of ether; Not miscible with light mineral oil or fixediols, but will dissolve some essential oils.
Specific heat	2.47 J/g (0.590 cal/g) at 20°C
Surface tension	40.1 mN/m (40.1 dynes/cm) at 25°C
Vapor density (relative)	2.62 (air=1)
Vapor pressure	9.33 Pa (0.07 mm Hg) at 20°C
Viscosity (dynamic)	58.1 mPa s (58.1 cP) at 20°C

Table 6: Various properties of lactic acid

Boiling point	**122°C at 2 kPa (15 mm Hg)**
Dissociation constant	pKa = 4.14 at 22.5°C
Flash point	>110°C
Heat of combustion	15.13 kJ/kg (3615 cal/kg)
Melting point	17°C
Osmolarity	A 2.3% w/v aqueous solution is iso-osmotic with serum
Refractive index	n^{20}_{D} = 1.4251
Solubility	Miscible with ethanol (95%), ether and water; Practically insoluble in chloroform
Specific heat	2.11 J/g (0.505 cal/g) at 20°C
Specific gravity	1.21
Specific rotation	$[\alpha]^{21}_{D}$ = −2.6°C (8% w/v aqueous solution) for (R)-form; = +2.6°C (2.5% w/v aqueous solution) for (S)-form
Viscosity (dynamic)	28.5 mPa s (28.5 cP) for 85% aqueous solution at 25°C

Table 7: Various properties of gelatin

Acidity/alkalinity	For a 1% w/v aqueous solution at 25°C (depending on source and grade) pH=3.8–5.5 (type A) pH=5.0–7.5 (type B)
Density	1.32 g/cm^3 for type A 1.28 g/cm^3 for type B
Isoelectric point	7.0–9.0 for type A 4.7–5.4 for type B
Moisture content	9–11%
Melting point	167°C
Glass transition temperature	57°C

Table 8: Various grades of gelatin and viscosity

Various grades of gelatin and viscosity	**Viscosity (dynamic) mPa s**	
	6.67% w/v aqueous solution	**12.5% w/c aqueous solution**
Acid ossein	2.7–3.7	12.5–14.5
Acid pigskin	4.2–4.8	19.0–20.5
Fish skin	3.0–4.5	13.0–20.0
Lime ossein/hide	3.6–4.8	19.0–20.5

Table 9: Various typical properties of glycerin

Boiling point	290°C (with decomposition)
Density	1.2656 g/cm^3 at 15°C 1.2636 g/cm^3 at 20°C 1.2620 g/cm^3 at 25°C
Flash point	176°C (open cup)
Hygroscopicity	Hygroscopic
Melting point	17.8°C
Osmolarity	A 2.6% v/v aqueous solution is iso-osmotic with serum
Refractive index	n^{15}_{D}=1.4758 n^{20}_{D}=1.4746 n^{25}_{D}=1.4730
Surface tension	63.4 mN/m (63.4 dynes/cm) at 20°C
Vapor density (relative)	3.17 (air=1)
Specific gravity	at 20°C 1.024 for 10% w/w glycerin solution
Viscosity (dynamic)	1.311(mPa s) at 20°C for 10% w/w aqueous glycerine solution
Freezing point	1.6 for 10% w/w aqueous glycerine solution

- Dissimilarity or difference factor (f1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves. The percent error is zero when the test and reference release profiles are identical and increases proportionally with the dissimilarity between the two profiles.
- There are several methods for dissolution profile comparison. f2 is the simplest among those methods. Moore and Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f1 and f2.

Table 10: Chemical composition of various grades of sorbitol special

Chemical component	USP/EP specification	Sorbitol special typical levels	Sorbitol special MDF 85 typical levels
1,4-sorbitan (dry base)	NLT 15%	21–7%	26–35%
Sorbitol (dry base)	NLT 25%	60–67%	33–59%
Mannitol (dry base)	No specific	2–4%	1–6%
High polychains	No specific	<1%	23–25%
Water	NMT 31.5%	Approximately 23%	Approximately 15%

Table 11: List of the materials used for medicament preparation

Name	Category	Manufacturer
NSAID drug	Non-steroidal anti-inflammatory Agent	Jai Radhe Sales
Polyethylene glycol-400	Hydrophilic solvent	DMV Fontera
Propylene glycol	Co-solvent	Merck
Povidone k 12 Povidone k 17 Povidone k 30	Re-crystallization inhibitor	ISP
Lactic acid	pH modifier	Merck
Purified water	Vehicle	CELON Labs

Table 12: List of the materials used for gelatin mass preparation

Name	Category	Manufacturer
Gelatin 160 Bloom Gelatin 180 Bloom	Film forming agent	Merck
Glycerin	Plasticizer	Merck
Sorbitol special	Plasticizer	Merck
FD&C Blue No. 1	Coloring agent	BASF
Purified water	Vehicle	CELON Labs

$$f1 = \{[\sum_{t=1}^{n} | Rt - Tt |] / [\sum_{t=1}^{n} Rt]\}.100$$

$$f2 = 50.\mathrm{Log}\{[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5}.100\}$$

Where "R_t" and "T_t" are the cumulative percentage dissolved at each of the selected n time point of the reference and test product, respectively. The factor f1 is proportional to the average difference between the two profiles, whereas factor f2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points.

Table 13: List of the equipments used

Equipment	Manufacturer	Model no.
Electronic Balance	Shimadzu	AUX220
Sieves	United Engineering Ltd.	ASL00
pH-Meter	Eutech	PH-1500
Vernier calipers	Mitutoyo	TD-6T
Colloidal mill	Cadmach	PMC-CM
Laboratory Stirrer	Remi	RQT-124A
UV	Shimadzu	UV1800
Viscometer	Brookfield	DV-II
Dissolution test apparatus	Labindia	Disso 2000
Stability chambers	Thermolab	Standard
Disintegration tester	Electrolab	ED-2L
Hardness tester	Barries	Barries
Encapsulation machine	Arbes	Arbes-X-8
FT-IR	Perkin elmer	L1600107

The similarity factor f2 and its significance are shown in the following table.

Stability studies

The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air, etc.). The final formulation was packed in suitable packing such as blister and strip packs or in HDPE containers and then they will be kept at different temperature, humidity conditions and the samples were analyzed for their physical and chemical properties.

The stability studies were carried out according to ICH guidelines for the optimized formulation, that is, F-8. The stability studies were carried out under accelerated stability conditions (40±2°C/75% ±5% RH). The softgel capsules were packed in 40cc HDPE containers packing and then stored under three conditions. Sample were collected at an interval of 1, 2, and 3rd months and evaluated. Dissolution profile of F-8 stored at three conditions in 1M, 2M, and 3M samples was found to be similar with that of initial samples.

DISCUSSION

The aim of the present work is formulation and evaluation of liquid filled soft gelatin capsules

Table 14: Drug-excipient compatibility studies

Ingredients	Ratio	Qty of blend (g)
API	1	1.1
API+purified water	1:0.23	1.353
API+PEG 400	1:3.18	4.598
API+PEG 600	1:3.18	4.598
API+Povidone K 12	1:0.23	1.353
API+Povidone K 30	1:0.23	1.353
API+Povidone K 17	1:0.23	1.353
API+Lactic acid	1:0.28	1.408
API+propylene glycol	1:0.23	1.353
API+Lactic acid+purified water	1:0.28:0.23	1.661
API+PEG 400+PEG 600+Propylene glycol+PVP K12+PVP K17+PVP K30+Lactic acid+purified water+Gelatin shell	1:3.18:3.18:0.23:0. 23:0.23:0.23:0.28:0.23:1.95	11.814
API+PEG 400+Propylene glycol+PVP K30+Lactic acid+purified water+Gelatin shell	1:3.18:0.23:0.23:0.28:0.23:1.95	7.810
API+PEG 400+Propylene glycol+PVP K12+Lactic acid+purified water+Gelatin shell	1:3.18:0.23:0.23:0.23:0.28:1.95	7.810
API+PEG 400+Propylene glycol+PVP K17+Lactic acid+purified water+Gelatin Shell	1:3.18:0.23:0.23:0.23:0.28:1.95	7.810
API+PEG 600+Propylene glycol+PVP K30+Lactic acid+purified water+Gelatin shell	1:3.18:0.23:0.23:0.28:0.23:1.95	7.810
API+PEG 600+Propylene glycol+PVP K17+Lactic acid+purified water+Gelatin Shell	1:3.18:0.23:0.23:0.28:0.23:1.95	7.810
API+PEG 600+Propylene glycol+PVP K12+Lactic acid+purified water+Gelatin shell	1:3.18:0.23:0.23:0.28:0.23:1.95	7.810
PEG 400+PEG 600+Propylene glycol+PVP K12+PVP K30+Lactic acid+purified water+Gelatin shell	3.18:3.18:0.23:0.23:0.23:0.28:0.23:1.95	10.484
PEG 400+Propylene glycol+PVP K30+purified water+Lactic acid+Gelatin shell	3.18:0.23:0.23:0.23:0.28:1.95	6.710
PEG 400+Propylene glycol+PVP K12+purified water+Lactic acid+Gelatin shell	3.18:0.23:0.23:0.23:0.28:1.95	6.710
PEG 400+Propylene glycol+PVP K17+purified water+Lactic acid+Gelatin shell	3.18:0.23:0.23:0.23:0.28:1.95	6.710
PEG 600+Propylene glycol+PVP K30+purified water+Lactic acid+Gelatin shell	3.18:0.23:0.23:0.23:0.28:1.95	6.710
PEG 600+Propylene glycol+PVP K12+purified water+Lactic acid+Gelatin shell	3.18:0.23:0.23:0.23:0.28:1.95	6.710
PEG 600+Propylene glycol+PVP K17+purified water+Lactic acid+Gelatin shell	3.18:0.23:0.23:0.23:0.28:1.95	6.710
Gelatin shell (Gelatin+Glycerin+Sorbitol special+FD&C Blue No. 1+purified water)	1.95	2.145
API+Gelatin shell	1:1.95	3.465

Table 15: Table for solubility terminologies

Descriptive term (solubility definition)	Parts of solvent required the for one part of solute	Solubility assigned (mg/ml)
Very soluble	<1	1000
Freely soluble from	1–10	100
Soluble from	10–30	33
Sparingly soluble from	30–300	10
Slightly soluble from	100–1000	1
Very slightly soluble from	1000–10000	0.1
Practically insoluble	≥10000	0.01

NSAID drug, to increase the bioavailability and rapid onset of action. The basic goal of formulation is to enhance the bioavailability and non-toxic within a short period of time due to rapid onset of action of the designed formulation. The design of proper dosage form is an important element to accomplish this goal. NSAID drug is one of the most important nonsteroidal anti-inflammatory agents used in the treatment of acute to chronic pain. NSAID drug is a BCS Class-II drug, so as to enhance its solubility and bioavailability it is formulated as a liquid filled soft gelatin capsule because liquid filled soft gelatin capsules of NSAID drug shows more bioavailability compared to other oral solid dosage forms. From the literature survey NSAID drug belongs to class BCS Class–II from the preformulation studies of API such as organoleptic properties described in Table 20. Melting point values of pure drugs are within the specification limit. The solubility of the NSAID drug is studied over different media and pH ranges described in Table 21, it is showing pH dependent solubility. The results of drug – excipient interaction study indicated that the drug was stable

Table 16: Table for preliminary optimization trails

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Medicament solution preparation								
Naproxen sodium USP	220	220	220	220	220	220	220	220
PEG-400	632	585	630	615	620	616	627.5	616
Propylene glycol	40	35	24	42	43	33.25	40	47
Povidone K-12	50	-	-	-	40	-	-	-
Povidone K-17	-	50	-	-	-	47.5	-	-
Povidone k-30	-	-	50	34	-	-	25	28
Lactic acid	38	40	26	39	27	33.25	37.5	39
Total weight	980	930	950	950	950	950	950	950
Ingredients	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**
Gelatin mass preparation								
Gelatine USNF (Gelatine 160bloom)	243.6	232	223.88	228.8	-	-	-	-
Gelatine USNF (Gelatine 180 bloom)	-	-	-	-	225.5	218.4	228.8	223.2
Sorbitol surbiton solution USNF	81.2	92.8	75.4	90.45	66	78.4	90.45	73.45
Glycerin USP	46.4	34.8	42.2	33.9	55	49.8	33.9	50.85
FD&C Blue No-1 IH	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Purified water USP	208.74	220.34	218.46	211.79	203.45	218.34	211.79	217.44
Total weight	580	580	560	565	550	565	565	565

Table 17: Table for in-process parameters

In-process parameters	
Parameters	**Limits**
Description	Blue colored, transparent, oblong shaped soft gelatin capsules containing clear, pale yellow viscous liquid
Ribbon thickness	0.90 mm±0.05 mm
Average fill weight	930 mg±2% (911.4 mg–948.6 mg)
Gelatin shell weight	575 mg±10% (517.5 mg–632.5 mg)
Gross weight of capsules	1505 mg±3% (1459.85 mg–1550.15 mg)
Uniformity of fill weight	± 3% of average weight

Table 18: Table for in-process parameters for dried capsules

In-process parameters for dried capsules	
Parameters	**Limits**
Description	Blue colored, transparent, oblong shaped soft gelatin capsules imprinted as "NPX220" with black edible ink, containing clear pale yellow to pale blue coloured viscous liquid
Average weight of capsule	1340 mg±5% (1273 mg–1407 mg)
Average fill weight	930 mg±5% (883.5 mg–976.5 mg)
Hardness	8–15 N
Disintegration time	NMT 30 min (as per USP) NMT 60 min (as per EP)
Uniformity of fill weight	± 5% of Target weight

Table 19: Interpretation of diffusional release mechanisms

"n"	Mechanism
0.5	Fickian diffusion (Higuchi Matrix)
0.5	Anomalous transport
1	Case-II transport (Zero-order release)
n>1	Super case-II transport

Table 20: Organoleptic properties of NSAID drug

Properties	Observation
Description	Crystalline powder
Color	white to creamy white
Odor	Odor less

Table 21: Saturation solubility of NSAID drug

Saturation solubility of NSAID drug	
Medium	**Solubility (mg/ml)**
0.01N HCl (pH 2.01)	0.015
0.1N HCl (pH 1.05)	0.014
pH 4.5 acetate buffer	0.064
pH 6.8 phosphate buffer	31.485
pH 7.4 phosphate buffer	242.95
Purified water (pH 5.62)	232.991

when stored at accelerated conditions. It was also observed that addition of excipients does not affect the stability of drug and the results are tabulated in Table 22. The calibration curve of NSAID drug was constructed using UV spectrophotometer in pH 7.4 phosphate buffer. The curve in Figure 14

Table 22: Physical observations of drug-excipient compatibility is tabulated as follows

Composition	Initial	Final observation		Composition
		40°C/75%RH		
		2 weeks	4 weeks	
API	White to creamy crystalline powder.	NCC	NCC	Compatible
API+purified water	White to creamy semisolid mass.	NCC	NCC	Compatible
API+PEG 400	A colorless liquid with suspended white particles.	NCC	NCC	Compatible
API+PEG 600	A colorless liquid with suspended white particles.	NCC	NCC	Compatible
API+Povidone K 12	White to creamy powder.	NCC	NCC	Compatible
API+Povidone K 30	White to creamy powder.	NCC	NCC	Compatible
API+Povidone K 17	White to creamy powder.	NCC	NCC	Compatible
API+Lactic acid	White to creamy semisolid mass.	NCC	NCC	Compatible
API+propylene glycol	White to creamy semisolid mass.	NCC	NCC	Compatible
API+lactic acid+purified water	White to creamy semisolid mass.	NCC	NCC	Compatible
API+PEG 400+PEG 600+Propylene glycol+PVP K12+PVP	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatin mass.	NCC	NCC	Compatible
K17+PVP K30+Lactic acid+purified water+Gelatin shell		NCC	NCC	Compatible
API+PEG 400+Propylene glycol+PVP K30+Lactic acid+purified water+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatin mass.	NCC	NCC	Compatible
API+PEG 400+Propylene glycol+PVP K12+Lactic acid purified water+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatin mass.	NCC	NCC	Compatible
API+PEG 400+Propylene glycol+PVP K17+Lactic acid+purified water+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatine mass	NCC	NCC	Compatible
API+PEG 600+Propylene glycol+PVP K30+Lactic acid+purified water+Gelatin Shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatin mass.	NCC	NCC	Compatible
API+PEG 600+Propylene glycol+PVP K17+Lactic acid+purified water+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatin mass.	NCC	NCC	Compatible
API+PEG 600+Propylene glycol+PVP K12+Lactic acid+purified water+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatin mass.	NCC	NCC	Compatible
PEG 400+PEG 600+Propylene glycol+PVP K12+PVP K30+Lactic acid+purified water+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatin mass.	NCC	NCC	Compatible
PEG 400+Propylene glycol+PVP K30+purified water+Lactic acid+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatin mass.	NCC	NCC	Compatible
PEG 400+Propylene glycol+PVP K12+purified water+Lactic acid+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatin mass.	NCC	NCC	Compatible
PEG 400+Propylene glycol+PVP K17+purified water+Lactic acid+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatine mass.	NCC	NCC	Compatible
PEG 600+Propylene glycol+PVP K30+purified water+Lactic acid+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatine mass.	NCC	NCC	Compatible
PEG 600+Propylene glycol+PVP K12+purified water+Lactic acid+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatine mass.	NCC	NCC	Compatible
PEG 600+Propylene glycol+PVP K17+purified water+Lactic acid+Gelatin shell	A light blue colored liquid with suspended white particles containing light blue with hue transparent gelatine mass.	NCC	NCC	Compatible
Gelatin shell (Gelatin+Glycerin+Sorbitol special+FD&C Blue No. 1+purified water)	A light blue with hue transparent gelatin mass.			
API+Gelatin shell	White particles containing light blue with hue transparent gelatin mass.			

NCC: No characteristic change with respect to control sample

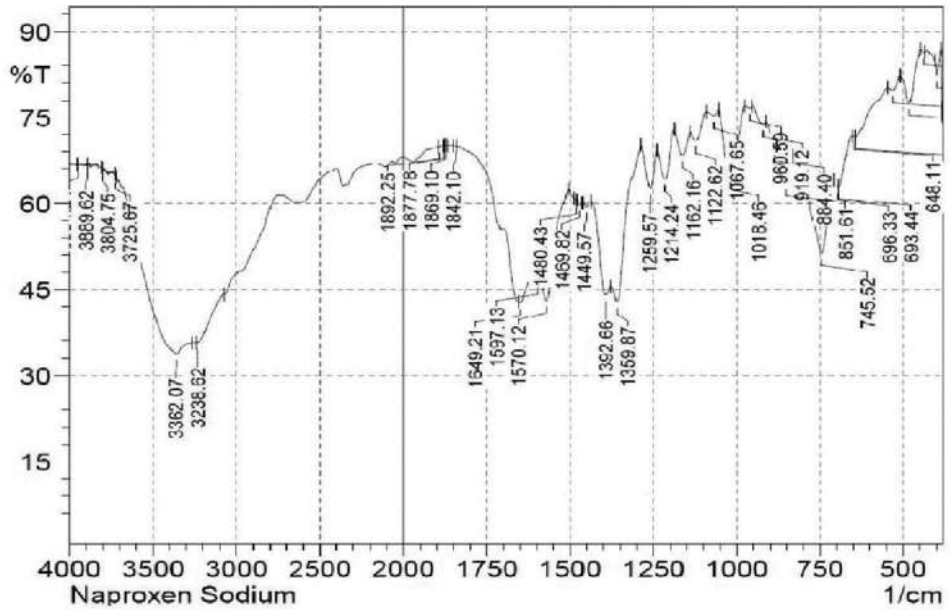

Figure 12: FT-IR spectra of NSAID drug

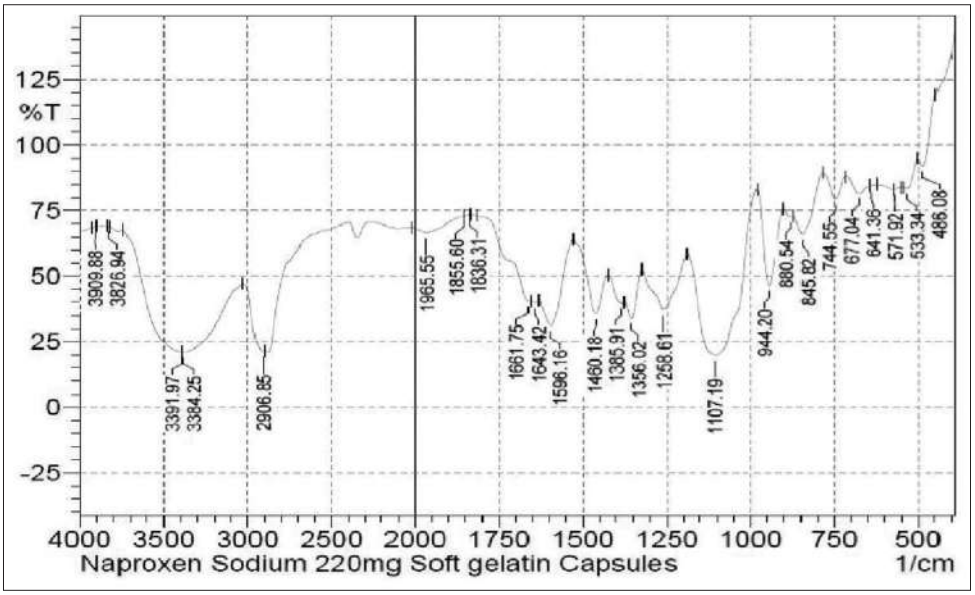

Figure 13: FTIR spectrum of physical mixtures of optimized formulation

Table 23: FT-IR peaks and their functional groups of NSAID drug

Functional group	Wave number (cm^{-1})
Usually sharp O-H	3362.07
C=C	1597.13
-CH3	1469.82
C-H	1392.66
C=O	1649.21

Table 24: Calibration curve of NSAID drug in pH 7.4 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
10	0.165
20	0.283
30	0.423
40	0.570
50	0.711

was found to be linear over a concentration range of 10–50 µg/ml and the R2 value is 0.998. The FTIR Spectrum of drug and combination of excipients in Figures 12 and 13 showed characteristic peaks for different functional groups such as, Aliphatic

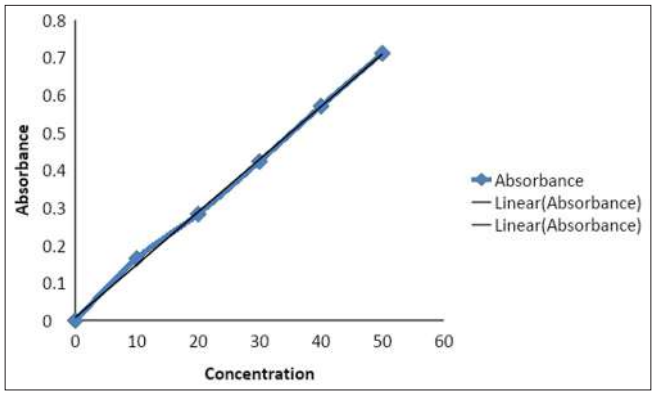

Figure 14: Calibration curve of NSAID drug in pH 7.4 phosphate buffer

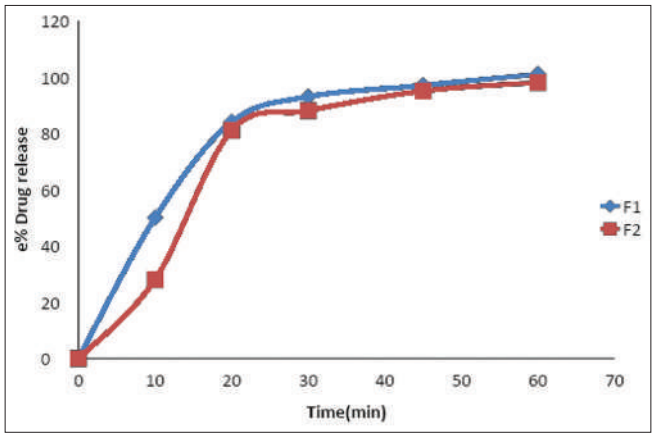

Figure 15: Comparison of *in vitro* dissolution profiles of formulations (F1-F2)

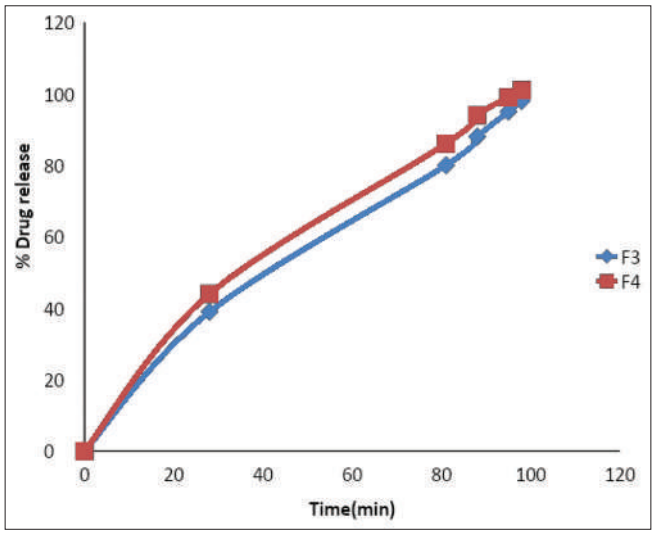

Figure 16: Comparison of *in vitro* dissolution profiles of formulations (F3-F4)

alkane C-H stretching, Phenolic O-H stretching, Aromatic C=C stretching. O-H stretching - 3200–

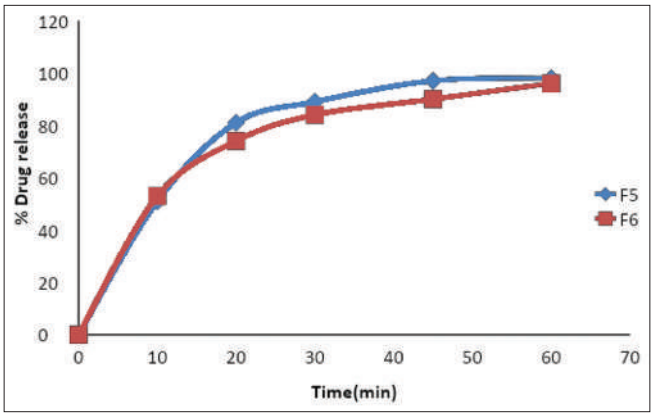

Figure 17: Comparison of *in vitro* dissolution profiles of formulations (F5-F6)

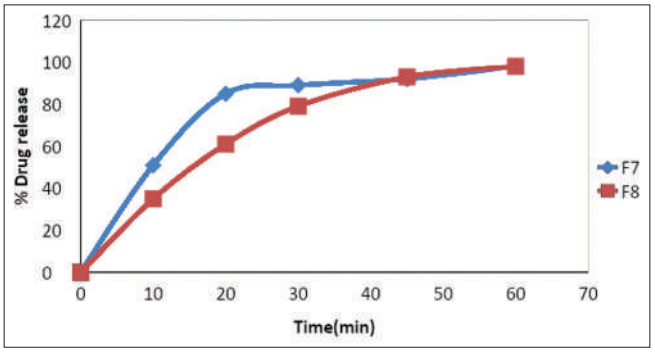

Figure 18: Comparison of *in vitro* dissolution profiles of formulations (F7-F8)

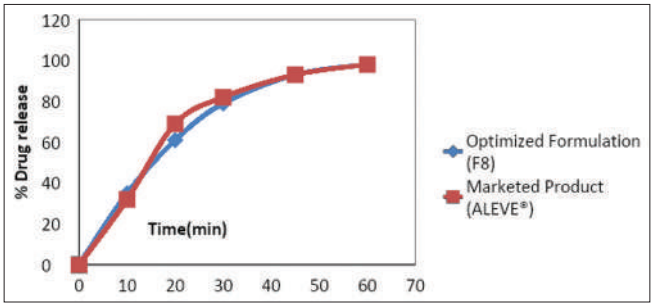

Figure 19: Comparison of *in vitro* dissolution profiles of formulations F(8) and marketed product

3550 cm^{-1} C-H stretching - 1440–1320 cm^{-1} C=C stretching - 1600–1500cm^{-1}.

In the IR spectra of drug mixed with excipients, the major peaks were retained indicating absence of interaction between the drug and various excipients. The FTIR data of pure drug and formulation indicated that there was no change in crystalline structure. No additional peaks were observed so it is evident that the pure drug NSAID drug is compatible with excipients.

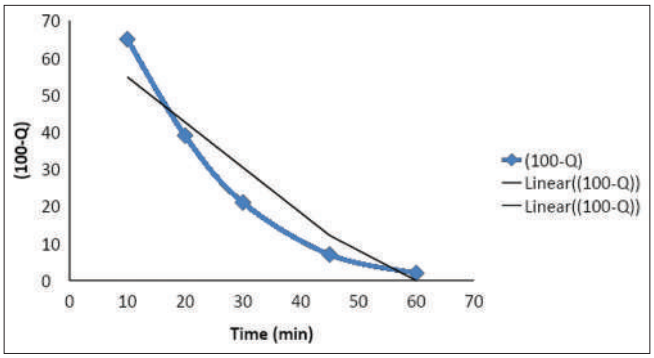

Figure 20: Zero-order kinetics plot of optimized formulation (F8)

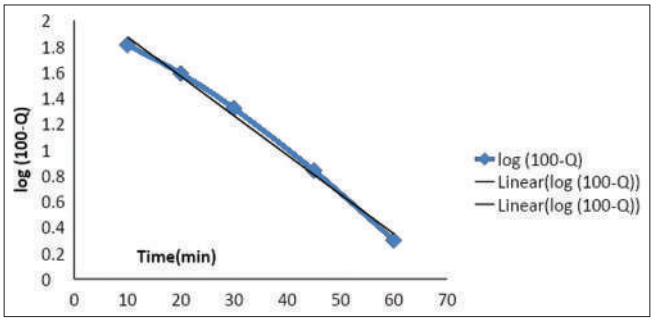

Figure 21: First-order kinetics plot of optimized formulation (F8)

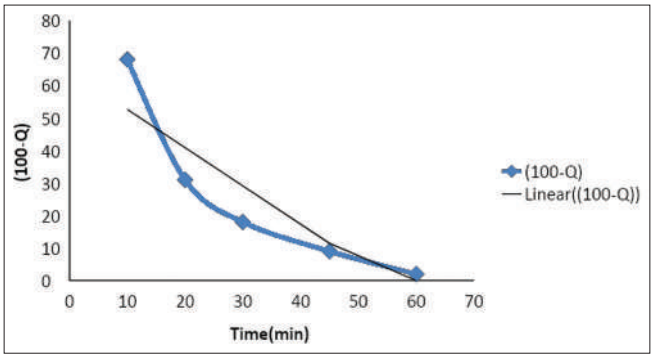

Figure 22: Zero-order kinetics plot of marketed product

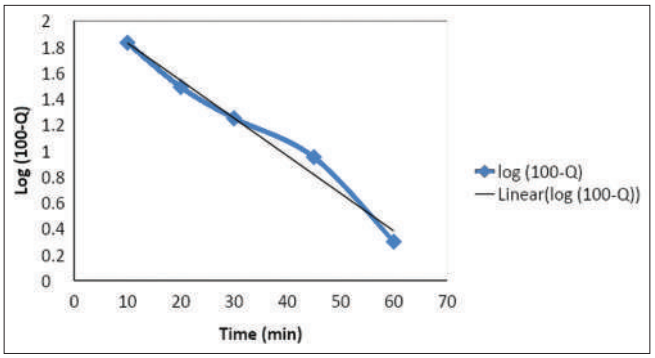

Figure 23: First-order kinetics plot of marketed product

Table 25: Soft gelatin capsules of formulations of trial batches

Formulation codes	Gross weight (mg)	Fill weight (mg)	Shell weight (mg)
F1	1537	885	652
F2	1495	931.5	563.2
F3	1498.0	939.2	558.2
F4	1498	939.2	558.2
F5	1504.4	934.2	570.2
F6	1504.0	929.4	574.4
F7	1498	934	574.4
F8	1508	933.3	574.4

Table 26: Encapsulation parameters during process

Encapsulation parameters	
Area temperature and humidity	25°C/32% RH
Gelatin tank temperature	60°C
Spreader box temperature	58°C
Segment temperature	37.5°C
cool drum temperature	9°C
Ribbon thickness	0.85–0.88
Fill weight (mg)	930.00 mg±3%
Shell weight (mg)	570.00 mg±10%
Gross weight (mg)	1500.00 mg±5%
Machine RPM	2 rpm
Die roll	14 minim oblongs
Temperature for drying in tray drier	NMT 23°C/20% RH

The intention of present study was to develop a product having similar release profile to the innovator product. Hence, the innovator product (ALEVE® Liquid filled capsules) was evaluated to determine the characteristics of final product are shown in Table 30. In this present study, (F1-F8) formulations have been designed to optimize the concentration of different excipients in the fill formulation and also gelatin shell formulation is shown in Table 29. Evaluation of the formulations F1-F8 such as weight variation, hardness, pH, disintegration time of all formulations with the specified limits are shown in Table 27. The drug content estimation F1-F8 shows lies between 96 and 105% as shown in the Table 28. From dissolution data Innovator and F8 was fitted with various kinetic models such as zero-order, first-order shown in Figure 21-23, respectively, the data were obtained linear for first-order kinetics. The correlation coefficient values (R2) of different kinetic models are given in Table 33. The R2value of first-order kinetics was more than

Table 27: Weight variation, hardness, and disintegration test of dried capsules

Formulation code	Weight variation			Hardness (N)	PH	Disintegration time (min)
	Gross weight (mg)	Fill weight (mg)	Shell weight (mg)			
F1	1443	887	556	7.8	7.2	13 min
F2	1404.2	950.4	455.8	8.2	7.5	13 min 27 s
F3	1374.2	956.7	417.5	8	7.6	12 min 28 s
F4	1368.1	954.5	414.4	8.5	7.55	14 min
F5	1372	951.1	420.4	8.2	7.45	13 min
F6	1375.4	944.6	430.8	8.2	7.4	14 min
F7	1379.2	955.2	424	8.4	7.4	14 min
F8	1375.4	961.4	414	8.5	7.42	13 min

Table 28: Drug content estimation of formulations trails (F1-F8)

Formulations code	% Drug content
F1	99.02
F2	100.12
F3	98.37
F4	99.21
F5	100.28
F6	99.37
F7	101.83
F8	99.75

Table 29: *In vitro* dissolution studies of formulations of (F1-F8)

TIME	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
10	50	28	39	44	51	53	51	35
20	84	81	80	86	81	74	85	61
30	93	88	88	94	89	84	89	79
45	97	95	95	99	97	90	92	93
60	101	98	98	101	98	96	98	98

Table 30: Dissolution profiles of marketed product and optimized formulation (F8)

Hours	Optimized formulation (F8)	Marketed product (ALEVE®)
0	0	0
10	35	32
20	61	69
30	79	82
45	93	93
60	98	98

Table 31: Similarity factor f2 and its significance

Similarity factor (f2)	Significance
<50	Test and reference profiles are dissimilar
50–100	Test and reference profiles are similar
100	Test and reference profiles are identical
>100	The equation yields a negative value

Table 32: Drug release kinetics of optimized formulation F8

Time (min)	Q	(100-Q)	log (100-Q)
10	35	65	1.81
20	61	39	1.59
30	79	21	1.32
45	93	7	0.84
60	98	2	0.3

Table 33: Order of drug release kinetics for formulation (F8)

Order of Kinetics	Zero-order	Frist-order
R2 values	0.887	0.992

Table 34: Drug release kinetics of marketed product

Time (min)	Q	(100-Q)	log (100-Q)
10	32	68	1.83
20	69	31	1.49
30	82	18	1.25
45	91	9	0.95
60	98	2	0.3

Table 35: ICH guidelines for stability study

Study	Storage condition	Time period
Long term	25±2°C/60%RH±5% RH	12 months
Intermediate	30±2°C/65%RH±5%RH	6 months
Accelerated	40±2°C/75%RH±5%RH	6 months

that of the zero-order. The graph of time versus log cumulative percentage drug remained found to be linear with the linearity R2= 0.992 indicating that it followed first-order release kinetics. Stability studies were done on final optimized formulation F8 to determine the odor, color change, dissolution

Table 36: Stability studies of optimized formulation (F8)

Sample type	Sampling interval	F8 formulation					
		Room temperature			40°C±2°C/75% RH		
		Color	Odor	Assay	Color	Odor	Assay
Closed container	0 month	No Color Change	No odor	99.75	No Color Change	No odor	99.75
	1 month	No Color Change	No odor	99.7	No Color Change	No odor	100.6
	2 month	No Color Change	No odor	98.6	No Color Change	No odor	99.2
	3 month	No Color Change	No odor	98.5	No Color Change	No odor	98.4

Table 37: Comparison of drug release profile of initial and stability batches of optimized formulation (F8)

Time (h)	Initial	1st month	2nd month	3rd month
10	35	35	36	37
20	61	63	61	61
30	79	78	80	80
45	93	94	97	96
60	98	95	98	98

profile, and assay of drug during storage conditions and it was found to be stable according to the data shown in Table 3 and 36.

SUMMARY AND CONCLUSION

Summary

The basic goal of formulation is to achieve an enhanced bioavailability that is therapeutically effective and non-toxic, when compared to other oral solid dosage forms. The design of proper dosage form is an important element to accomplish this goal. One such area of research is design of Softgel technology. Softgel technology is one of the most attractive and promising approach for increasing oral bioavailability by means of increasing solubility of the poorly soluble drug. NSAID drug is one of the most important Non-steroidal anti-inflammatory agents used in the treatment of acute to chronic pains, inflammation and it belongs to BCS Class-II drug so as to increase its aqueous solubility for enhancing the bioavailability, it is formulated as a liquid filled soft gelatin capsules. The objective of this present work is to develop an immediate release formulation of by NSAID drug using Softgel technology; the fill formulation is prepared and encapsulated by using a gelatin shell. Pre-formulation study was performed by formulating binary mixtures of drug with selected excipients. Binary mixtures were screened for physical appearance at initial and 40°C ± 2°C / 75% ± 5% RH, 4 weeks in close condition. Physical observations of binary mixtures and FTIR study revealed that there is no incompatibility between NSAID drug and selected excipients in the formulation, when exposed to accelerated stability condition of 40°C/75%RH for 1 month. UV spectrophotometric analytical method was developed for the model drug in pH 7.4 Phosphate buffer. Absorption maxima were found to be at 272 nm and the linearity was fixed between the ranges of 10–50 μg/ml. Various physical properties of like hardness, surface characteristics, practical size, pH weight variation, and rupture time can significantly affect the rate of dissolution of drugs contained in a formulation. Various formulation trials of NSAID drug soft gelatin capsules were developed using various excipients for aqueous based fill formulation and gelatin shell formulation. Results of evaluation parameters such as hardness, weight variation, pH of fill medicament, assay, disintegration test, and encapsulation parameters were evaluated. Observations of all formulations for physical

characterization had shown that, all of them comply with the specifications of official pharmacopoeias and/or standard references. The formulations were optimized for binder, re-crystallization inhibitor, solubilize, pH modifier for fill formulation and plasticizer, different bloom strength of gelatine for gelatin shell formulation, and evaluating different trials (F1-F8). Formulation F8 had showed better release profile which is similar to drug release of marketed product. The *in vitro* drug release data obtained were extrapolated by zero-order, first-order to know the mechanism of drug release from the formulations. The release kinetics shows that the release of drug followed first-order release in all the formulations. As the drug release was best fitted in first-order kinetics, indicating that the rate of drug release is dependent on concentration.

CONCLUSION

- The objective of the present study is to formulate and evaluate NSAID drug soft gelatin capsules.
- The pre-formulation studies have been conducted for API. From the solubility studies it revealed that NSAID drug shows poor solubility in various media and pH ranges it shows pH dependent solubility.
- The FTIR studies revealed that the drug and excipients does not show any characteristically changes in the peak and compatible.
- Using optimization method, the concentrations of lactic acid, Povidone, propylene glycol and water in the fill formulation, glycerin, sorbitol special, and gelatin in gelatin shell formulation were optimized.
- From the above observations, it can be concluded that combination of lactic acid, Povidone, propylene glycol, water, PEG 400, glycerin, sorbitol special, and gelatin has shown effective release of NSAID drug by increasing solubility and enhancing bioavailability.
- Hence, it can be evident that by formulating the NSAID drug soft gelatin capsules by softgel technology which results in more effective release of drug, increased solubility and oral bioavailability may also be enhanced.

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