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Novel Composition Comprising Poorly Water Soluble or Water Insoluble Actives and Their Solubility and Dissolution Enhancement

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Abstract:
The present work relates to improving water solubility of poorly water soluble and insoluble actives. More specifically, it relates to improving the aqueous solubility of a variety of materials produced for the pharmaceutical industries. One of the biggest challenges facing the pharmaceutical and biotechnology industries at present is the poor solubility of new and established chemical entities. There are many poorly soluble pharmaceutically active agents which could be formulated in accordance with the present study. It is an object of the study to provide an improved formulation for poorly water soluble or water insoluble active substances, which has improved bioavailability.

Keywords: Solubility, dissolution, bioavailability, formulation

Introduction

It is estimated that up to 90% on new molecular entities and 40% of existing compounds can be categorised as BCS class II or IV, which means that they show poor and variable oral bioavailability in vivo (Ref 1). Due to their low dissolution rate and poor bioavailability, hydrophobic drugs are challenging to administer and formulate.

Solubility enhancement can be achieved by either physical and/or chemical modification of the drug. Various techniques are available for solubility enhancement of poorly soluble drugs include particle size reduction, salt formation, solid dispersions, use of surfactants, prodrug, crystal modification, etc. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development.[1]

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution.[2]

IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units. Saturated solutions of ionic compounds of relatively low solubility are sometimes described by solubility constants. It is a case of equilibrium process. It

describes the balance between dissolved ions from the salt and undissolved salt. Similar to other equilibrium constants, temperature would affect the numerical value of solubility constant. The value of this constant is generally independent of the presence of other species in the solvent.

Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability active agents include: Enhancing solubility and dissolution rate of poorly water- soluble drugs and enhancing permeability of poorly permeable drugs. These two areas form the basis of the biopharmaceutical Classification system (BCS) which is incorporated in the guidelines of the Food and Drug Administration (FDA). The Biopharmaceutical Classification System (BCS) was originally proposed in 1995 by Amidon et al. It serves as a scientific framework used to review and classify drugs based on aqueous solubility, intestinal permeability and dissolution rate. BCS is a commonly used tool in drug development to determine the correlation of solubility and permeability with the bioavailability of drugs. Drugs can be categorized into four Biopharmaceutical classes based on solubility, permeability and invitro dissolution. All drugs have been divided into four classes: class I—high soluble and high permeable, class II—low soluble and high permeable, class III—low soluble and high permeable and class IV—low soluble and low permeable.[3]

Various techniques have been employed thus far for improving the solubility and consequently the bioavailability of poorly soluble drugs especially those belonging to BCS class II.

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, costeffectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products.

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Solubility also plays a major role for other dosage forms like parenteral formulations as well. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.[5]

For a drug to be properly absorbed by the body, it needs to be in a solution state at the point of absorption. The solubility of a drug is crucial to ensure the right concentration of a drug gets into the bloodstream so the bioavailability of the drug causes the desired pharmacological response. Solubility is a key factor in determining how effective a new drug solution will be. Solubility enhancement techniques can help.[6]

Novel solubility enhancements include:[7]

1. **Liquisolid Technique –** Many drug candidates are lipophilic and with low water solubility, making dissolution and bioavailability a challenge. With the liquisolid technique, liquid medications are converted into dry, non-adherent, free flowing and compressible powder mixtures. This is done by

blending the liquid drug components with appropriate excipients, often known as carriers or coating materials.

2. **Spherical Agglomeration –** The spherical crystallization (SC) technique using the spherical agglomeration (SA) method is an agglomeration process that transforms crystals into a compacted spherical form during the crystallization stage. This reduces tablet size by eliminating the use of large amounts of fillers and improves flowability and compression characteristics of active pharmaceutical components.
3. **Melt Sono Crystallization –** A particle engineering technique used to modify the physicochemical and biopharmaceutical properties of drug Rosiglitazone-(RS)-5-{4-(2[methyl (pyridine-2-yl)amino]ethoxy benzyl]thiozolidione-2-4-dione, Melt sono crystallization (MSC) works as an insulin sensitizer, by binding to the pPAR receptor in fat cells and making the cells more responsive to insulin.
4. **The Prodrug Approach –** Prodrugs are inactive, bio reversible by-products of active drug molecules that must be transformed in vivo to unlock the active parent drug, which leads to the desired pharmacological effect in the body. Prodrug development can be very challenging, but it represents a feasible way to improve the erratic properties of drugs in development or already on the market.
5. **Nanotechnology Approaches –** Solubility can be improved by formulating drug compounds into nanoparticles with high specific surface areas, which aids in solubility and increases dissolution rate. If a solid dosage form is desired, the nanoparticles are stabilized by adsorption onto polymer carriers – a process conducted by fluid bed coating. Alternatively, the nanoparticles can be prepared as a suspension and administered as a liquid – either orally or by injection.[8]

Table 1: USP and BP solubility criteria

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Fenofibrate was first synthesized in 1974, as a derivative of clofibrate, and was initially offered in France. It was initially known as procetofen, and was later renamed fenofibrate' to comply with World Health Organization International Nonproprietary Name guidelines.

Fenofibrate, a Biopharmaceutics Classification System (BCS) class II drug, is very lipophilic (log P=5.24)3 and virtually insoluble in water. An orally administered agent possessing aqueous solubility <0.1 mg/mL usually demonstrates very poor absorption, owing to impaired aqueous solubility and dissolution rate. Fenofibrate has melting point 79-82°C.[9]

Fenofibrate is currently marketed as tablets under the trade names Tricor™, Fenoglide® and Triglide® and as capsules under the trade names Antara® and Lipofen® . Fenofibrate is poorly soluble in water and consequently has limited bioavailability. The drug has poor solubility in gastrointestinal fluid and consequently is poorly absorbed. Ibuprofen (iso-butyl-propanoic-phenolic acid) is a non-steroidal anti-inflammatory drug (NSAID) used for pain relief, fever reduction, and for reducing swelling. It has an antiplatelet effect, which is relatively mild and short-lived compared with aspirin or prescription antiplatelet drugs. In general, ibuprofen also has a vasodilation effect. Ibuprofen is available under a variety of trademarks, such as Motrin, Nurofen, Advil, and Nuprin.[10]

Bioavailability is the degree to which an active ingredient, after administration becomes available to the target tissue. Poor bioavailability poses significant problems in the development of pharmaceutical compositions. Active ingredients that are poorly soluble in aqueous media often have insufficient dissolution and consequently have poor bioavailability within an organism after oral administration. If solubility is low there may be incomplete and/or erratic absorption of the drug on either an intra-patient or inter-patient basis. In order to circumvent this disadvantage, the administration of multiple therapeutic doses is often necessary.

In recent years, focus in formulation laboratories for improving the bioavailability of hydrophobic pharmacologically active ingredients has been upon reducing particle size. The rate of dissolution of a particulate drug can be increased, by decreasing particle size, through an effective increase in surface area.[11]

Considerable effort has been made to develop methods for controlling drug particle size in pharmaceutical compositions. For example, in order to improve the rate of dissolution of fenofibrate, a wide variety of formulation methods have been employed, including micronization of the active principle, addition of a surfactant and co-micronization of fenofibrate with a surfactant.[12]

Materials and Methods

Fenofibrate and Ibuprofen were received as a gift sample from Alkem Lab. Maisine 35-1 (Hydrophobic component)was obtained from *Gattefosse*, Kolliphor RH40 (Surfactant) was obtained from BASF, Gelatin (carrier) was obtained from Nitta Gelatine India Ltd. All other chemicals were of analytical grade and used as received

Preparation of immediate release formulation

The composition is formulated as seamless spheres comprising

a. a poorly soluble pharmaceutical agent;
b. a hydrophobic component
c. a carrier;
d. a surfactant.

Processing steps of composition:

(i) melted together the pharmaceutically active agent, the hydrophobic component and the surfactant at a temperature greater than the melting point of the agent to produce a solution;

(ii) dispersed gelatin in water in a ratio of 0.8 : 1 to 1.2 : 1 by weight and allowing it to swell;

(iii) added the solution produced in step (i) to the remaining quantity of] water which is maintained at a temperature just below its boiling point to form an emulsion;

(iv) Added the swollen gelatin to the emulsion of step (iii) and allowed the gelatin to dissolve.
The resultant mixture is processed to produce seamless, spherical beads of size 1.4-1.7mm in diameter. The mixture is processed using a Spherex™ technology seamless spherical microcapsule manufacturing device, to produce seamless spherical microcapsules.
To check dissolution profile; USP Apparatus I (Paddle) was used with Volume of media: 900 ml, Media temperature: 37°C.; and Paddle rotation speed: 75 rpm.

Results and Discussion

Bioavailability is the degree to which an active ingredient, after administration becomes available to the target tissue. Poor bioavailability poses significant problems in the development of pharmaceutical compositions. Active ingredients that are poorly soluble in aqueous media often have insufficient dissolution and consequently have poor bioavailability within an organism after oral administration. If solubility is low there may be incomplete and/or erratic absorption of the drug on either an intra-patient or inter-patient basis. In order to circumvent this disadvantage, the administration of multiple therapeutic doses is often necessary.

The present work provides an improved immediate release fenofibrate formulation, which has enhanced dissolution and absorption profiles. Advantages include reduced dose dumping, less variability in absorption compared to existing formulations, and much faster release and dissolution due to processing at the melt temperature of the drug, the minicapsule formulation and increased surface area of the spheres. Furthermore, the present invention does not require the addition of disintegrants to achieve this enhanced dissolution profile.

Hydrophobic component (e.g. a monoglyceride such as Maisine 35-1), a surfactant with a high HLB value (14-16) (e.g. Polyoxyl 40 hydrogenated castor oil, Tradename: Kolliphor RH40) and a carrier, preferably gelatin (either procine or bovine derived with bloom strength in the range 180-300). Poorly soluble drugs, Fenofibrate and Ibuprofen, having a low melting point were chosen to test the utility of the composition. The spheres have a diameter in the range of 0.5 mm to 7.0 mm.

The drug release profiles of the above formulations and the reference products (TRICOR® 48mg Fenofibrated tablets and Buplex® 200mg Ibuprofen tablets) was tested in biorelevant dissolution media; using Fasted State Simulated Intestinal Fluid (FaSSIF) for Tricor® and Fasted State Simulated Gastric Fluid (FaSSGF) for Buplex® . USP Apparatus I (Paddle) was used with Volume of media: 900 ml, Media temperature: 37°C.; and Paddle rotation speed: 75 rpm. Figure 1 shows the dissolution profiles for fenofibrate formulations; and Figure 2 shows the dissolution profiles for ibuprofen formulations of the present study.

Figure 1: Dissolution profiles for fenofibrate formulations

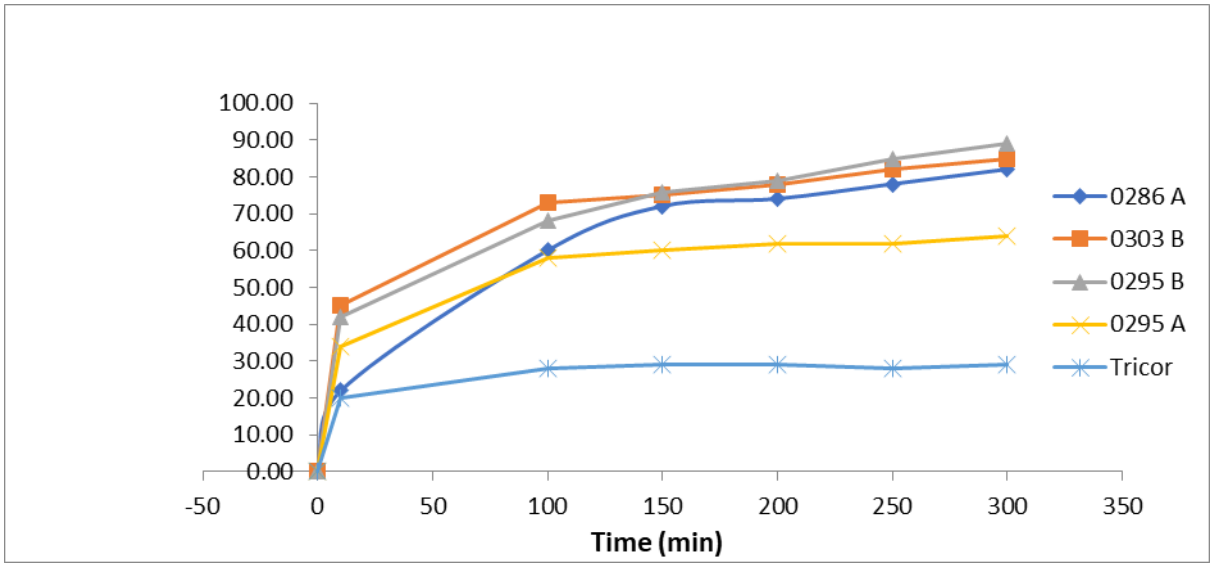
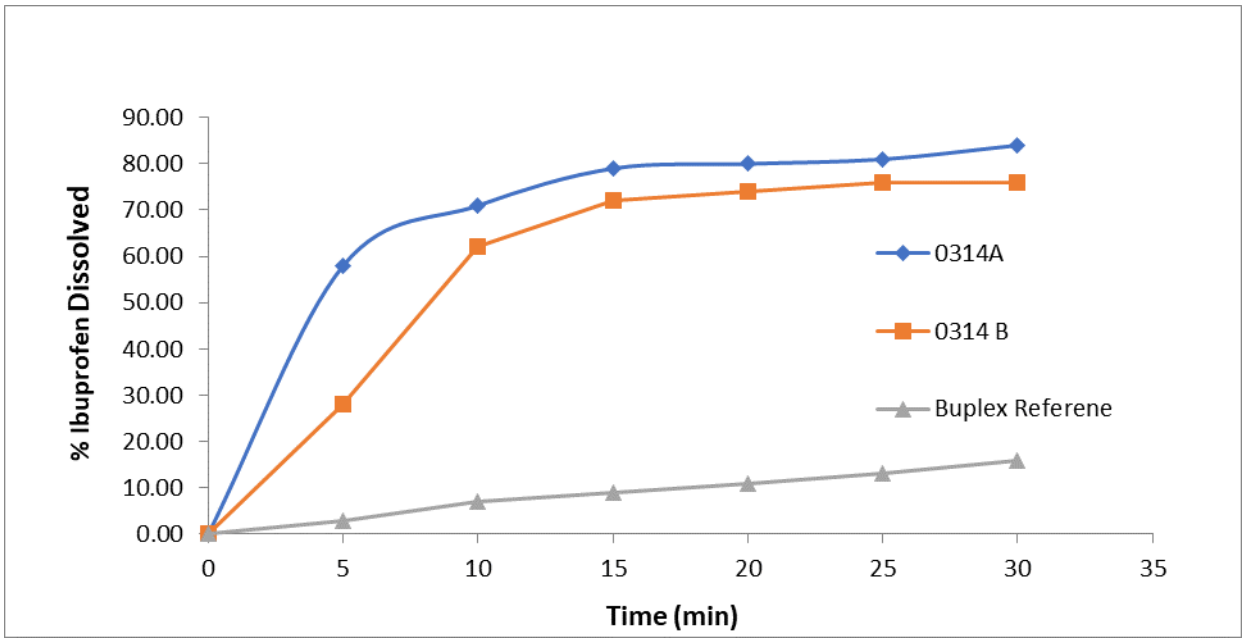


Figure 2: Dissolution profiles for ibuprofen formulations



A significant increase in % drug dissolved was observed with all formulations with respect to the prior art marketed products. In case of Fenofibrate, a 1:1.8 ratio of Maisine: Kolliphor proved optimal whereas with Ibuprofen, a 1:2.7 ratio of Maisine:Kolliphor showed higher dissolution than a 1:1.8 ratio.

Conclusion

Solubility plays a critical role in drug effectiveness. Without it, a drug substance cannot be absorbed, leading to low bioavailability. Poor solubility of drugs also leads to other issues, such as challenges with metabolism or permeability, interactions with other drugs or the need to extend drug release. Hydrophobic drugs may also suffer from food effects, erratic absorption and large variability in inter- and intra-patient dose response. While microemulsion preconcentrates have been used in the art to overcome some of these difficulties, they are often administered in a concentrated liquid or semi-solid form either as a drink solution or in a monolithic soft or hard elastic capsule. As is well known in the art,

monolithic dosage forms have several disadvantages including dose dumping, susceptibility to food intake, local irritation, variable gastric emptying and transit. In addition, drink solutions are not as acceptable to patients, are difficult to store and may be dosed irregularly by a patient. Due to their low dissolution rate and poor bioavailability, hydrophobic drugs are challenging to administer and formulate. The present study provided a pharmaceutical composition comprising: (a) a poorly soluble pharmaceutical agent; (b) a hydrophobic component, (c) a carrier; and (d) a surfactant. The poorly soluble pharmaceutical agent have a melting point of up to 100°C. A co-melt of the poorly soluble pharmaceutical agent with a hydrophobic component, a carrier and a surfactant is introduced as droplets into a cold hardening liquid. This rapid or quench cooling of the molten drug converts it into an amorphous state. Amorphous materials have higher free energy than their crystalline counterparts and as a result exhibit higher apparent solubility and faster dissolution rates. This inturn can lead to higher bioavailability of poorly-soluble drugs whose absorption is dissolution-rate limited. The final composition of the invention is a solid preconcentrate that upon oral intake, forms en emulsion (e.g. a microemulsion) when exposed to gastro-intestinal fluids. The invention functions by causing the amorphous drug to stay dissolved in the lipid or hydrophobic phase of the emulsion and/or in the micellar phase of the surfactant, thereby enhancing drug absorption and bioavailability.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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