

Challenges in testing of OINDPs

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Orally Inhaled and Nasal Drug Products (OINDPs) are the class of products that includes dry powder and metered dose inhalers (MDI), nebulizers and nasal sprays. Metered dose inhalers have grown in popularity since their introduction in the late 1950s, and are currently being used for treatment of a variety of diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and other lung diseases characterized by obstruction of airflow and shortness of breath. Metered dose inhaler products contain therapeutically active ingredients dissolved or suspended in a propellant, a mixture of propellants, or a mixture of solvents, propellants, and/or other excipients in compact pressurized aerosol dispensers. A MDI product may discharge up to several hundred metered doses of one or more drug substances. Depending on the product, each actuation may contain a few micrograms (mcg) up to milligrams (mg) of the active ingredients delivered in a volume typically between 25 and 100 microliters. Although similar in many features to other drug products, MDIs have unique differences with respect to formulation, container, closure, manufacturing, in-process and final controls, and stability. These differences need to be considered during the development program because they can affect the ability of the product to deliver reproducible doses to patients over the life of the product as well as the product's efficacy.

The use of NIDP's to deliver both locally acting and systemic therapies is on the increase; however, the regulatory requirements are challenging and in a constant state of evolution.

Many of the tests suggested by the regulators for ensuring the safety, quality and efficacy of OINDPs are common to all pharmaceutical dosage forms. Tests for leachables, extractables and microbial contaminants, for example, are mandatory for all inhaled products. Of the tests that specifically relate to OINDPs, delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) are universally

accepted as key parameters in assessing performance.

For all inhalation and nasal products containing a drug substance that is not in solution at any time during drug product manufacture, storage or use, the drug substance specification should include a particle size test and limits. A validated particle sizing method (e.g. laser diffraction), with acceptance criteria set at multiple points across the size distribution, should be employed. Acceptance criteria should assure a consistent particle size distribution in terms of the percentage of total particles in given size ranges. The median, upper, and/or lower particle size limits should be well-defined. Acceptance criteria should be set based on the observed range of variation, and should take into account the particle size distribution of batches that showed acceptable performance in vivo, as well as the intended use of the product. Process capability and stability data may also be considered, provided the proposed acceptance criteria have been suitably qualified.

Tests for Inhalation Products: The tests indicated below are normally conducted to characterise inhalation products. Not all tests are necessary for all types of inhalation products. However, any of the development tests may be applicable to any product, depending on the labelled instructions for use (e.g. shaking tests for certain dry powder inhalers). Moreover, depending on the operational characteristics of the delivery device, additional studies relevant to the performance of the drug product may be necessary.

Physical characterisation: Physical characteristics such as solubility, size, shape, density, rugosity, charge, and crystallinity of the drug substance and/or excipients may influence the homogeneity and reproducibility of the finished product. Development studies should include physical characterisation of drug substance and excipients, relevant to their effect on the functionality of the product. If

applicable, the effect of pre-processing the material (e.g. micronisation) on the physical characteristics should be evaluated.

Minimum Fill Justification: For metered dose inhalers and device-metered dry powder inhalers, a study should be conducted to demonstrate that the individual container minimum fill, as defined by the drug product manufacturing process, is sufficient to provide the labelled number of actuations. The final doses (as defined by the label claim) should meet the drug product specification limits for delivered dose uniformity and fine particle mass.

For pre-metered dry powder inhalers and products for nebulisation, the acceptance criteria for the fill volume and/or weight should be justified in relation to delivered dose uniformity and fine particle mass.

Extractables / Leachables: For non-compensial plastic and for rubber container closure components that are in contact with the formulation during storage (e.g. valves), a study should be conducted to determine the extractables profile. Details and justification of the study design (e.g. solvents used, temperature, storage time) and the results should be provided. It should be determined whether any of the extractables are also leachables present in the formulation at the end of the shelf life of the product or to the point equilibrium is reached, if sooner. The leachables profile should also be determined for compendial plastics and rubber container closure components. For compounds that appear as leachables, identification should be attempted and safety assessments should be conducted in accordance with adequately established safety thresholds. Depending on the levels and types of compounds detected, consideration should be given to including a test and limits for leachables in the drug product specification. If a correlation between extractable and leachable profiles can be established, control of leachables could be accomplished via testing and limits on extractables, either on the components or on the raw materials

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if a correlation has been shown between the levels in the raw materials and components. If there are no safety concerns with the type and level of leachables detected, routine monitoring of leachables would not be necessary.

Delivered dose uniformity and fine particle mass through container life: A study should be conducted to demonstrate the consistency of the minimum delivered dose (e.g. one or more actuations) and the fine particle mass through the life of the container from the first dose (post-priming dose for products with priming instructions) until the last labelled dose. The containers should be used and tested according to the information for the patient with respect to storage orientation and cleaning requirements, as well as minimum dosing interval. It is generally expected that at least ten doses from the combination of the beginning, middle, and end of the container be tested.

The doses obtained should meet the drug product specification limits for delivered dose uniformity and fine particle mass. Non-conforming results should be explained.

The doses between the last labelled dose and the last container exhaustion dose should also be tested for delivered dose uniformity and fine particle mass, and information on the tail-off profile should be provided where applicable. At least three containers from each of two different batches should be investigated. This testing may be waived if the container contains a lockout mechanism that prevents dosing beyond the labelled number of doses.

Delivered dose uniformity and fine particle mass over patient flow rate range: A study should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass over the range of flow rates (through the delivery device) achievable by the intended patient population, at constant volume. The range of flow rates should be justified in relation to clinical studies or published data for the same delivery device. The minimum (e.g. 10th percentile), median, and maximum (e.g. 90th percentile) achievable rate should be investigated.

Depending on the results of this study (e.g. if the minimum flow rate does not produce an acceptable dose), consideration should be given to providing information on the effect of flow rate on the performance of the product to health care professionals.

Fine particle mass with spacer/holding chamber use: For inhalation products that may be administered with a spacer or holding chamber, a study should be conducted to

determine whether the use of the spacer or holding chamber changes the fine particle mass. If the instructions accompanying the spacer or holding chamber include an in-use cleaning schedule (e.g., weekly cleaning), the fine particle mass should be tested before and after cleaning the spacer or holding chamber according to the instructions provided with the device. The fine particle mass test used for routine testing of the product may be altered to mimic patient performance with the spacer or holding chamber (e.g., a 2 second delay, tidal breathing). Any differences in fine particle mass should be assessed for their clinical relevance, with support from any clinical data obtained with the spacer or holding chamber.

Single dose fine particle mass: The fine particle mass should be routinely determined using the minimum recommended dose, if technically possible. If the fine particle mass test included in the drug product specification uses a sample size greater than the minimum recommended dose, a study should be conducted to demonstrate that the sample size used routinely provides results equivalent to those obtained using the minimum recommended dose. Justification should be provided for not conducting this test (e.g. for low dosed products) and for non-equivalent results. The fine particle mass of one dose should be determined according to the drug product specification fine particle mass method, modified only as necessary to accommodate the reduced sample size. Stage pooling prior to analysis is acceptable. The selection of the pooled stages should be justified. If this study is not feasible due to the sensitivity of the analytical method, data supporting this claim should be provided.

The results obtained should be compared to fine particle mass results obtained according to the unmodified fine particle mass method for the same batches. Any differences should be assessed for their significance.

Particle / droplet size distribution: To allow an assessment of the complete profile of the product used in in vivo (pivotal clinical and/or comparative) studies, individual stage particle size distribution data should be provided for the batches used in these studies, as well as data on batches representative of the commercial process. Using a multistage impactor or impinger, the drug mass on each stage and the cumulative mass undersize a given stage should be determined rather than the percentage of emitted dose (or other derived parameter) as these can hide variations in delivered dose. A plot of cumulative percentage less than a stated cut-off diameter versus cut-off diameter should usually be provided.

From this, the Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) may be determined, if appropriate (in the case of uni-modal log-normal distribution). Mass balance reconciliation should also be considered. When a range of different strengths is proposed, proportionality in fine particle mass and other size ranges (e.g., mass deposited in the impactor throat) should be considered. For solutions for nebulisation, droplet size distribution may be tested by other methods (e.g. laser diffraction).

Actuator / Mouthpiece deposition: The amount of drug deposited on the actuator or mouthpiece should be determined and, where applicable, demonstrated to be consistent with any correction factor used to support ex-valve (or ex-delivery device) label claims.

Drug delivery rate and total drug delivered: To allow an assessment of the complete delivery profile of the product used in in vivo (pivotal clinical and/or comparative) studies, the drug delivery rate and total drug delivered (i.e. total dose delivered to the patient) results should be provided for the batches used in these studies. A validated method (e.g. breath simulator), should be employed. The aerosol should be generated with the nebuliser system(s) and settings used in the in vivo studies.

Shaking requirements: For products requiring shaking before use (according to the instructions for use), a study should be conducted to demonstrate that the shaking instructions provided to the consumer are adequate. The possibility of excessive shaking leading to foaming and inaccurate dosing should be examined by testing the delivered dose uniformity.

Initial priming of the container: A study should be conducted to support the number of actuations recommended in the labelling that should be fired to waste (priming actuations) prior to the consumer using the product for the first time. Containers should be stored in various orientations prior to the initiation of the study in order to determine the effect of orientation. The length of storage prior to conducting the study should be indicated and justified. The number of priming actuations required until the subsequent doses meet the drug product specification limits for delivered dose uniformity should be determined. Priming instructions should be provided to the health care professional and the consumer.

Re-priming of the container: A study should be conducted to support the length of time that the product may be stored

without use (after initial priming) before re-priming as recommended in the labelling, as well as the number of repriming actuations required. Containers should be stored in various orientations prior to and during the study in order to determine the effect of orientation. The need to test products at different stages through container life should also be considered. Multiple time points should be used. The number of re-priming actuations required until the subsequent doses meet the drug product specification limits for delivered dose uniformity should be determined. Re-priming instructions, including any necessary instructions with respect to storage orientation, should be provided to the health care professional and the consumer.

Cleaning requirements: Delivered dose uniformity and fine particle mass or droplet size distribution data to support the recommended cleaning instructions provided to the health care professional and the consumer (including method and frequency) should be provided. The study should be conducted under conditions of normal patient usage, in accordance with recommendations for priming, dosing intervals, and typical dosing regimen.

Low temperature performance: A study should be conducted to determine the effect of low temperature storage on the performance of the product. Containers should be stored in various orientations for at least 3 hours at a temperature below freezing (0°C), and then immediately tested. The number of actuations required until the subsequent doses meet the drug product specification limits for delivered dose uniformity and fine particle mass should be determined. If the product does not perform satisfactorily (e.g., re-priming actuations required exceed the number required according to the instructions for use), an additional study should be conducted to determine the method and length of time needed to adequately warm the containers so that satisfactory performance is achieved. Instructions regarding cold temperature use should be provided to the health care professional and the consumer. If this study is not conducted, information on how and how long to warm the container should be provided to the health care professional and the consumer. Alternative approaches for inhalation products which do not tolerate low temperatures should be fully justified.

Performance after temperature cycling: A study should be conducted to determine the effect of temperature cycling on the performance of the product. Containers should be stored in various

orientations and cycled between recommended storage conditions and a temperature below freezing (0°C). For suspensions, cycling between the recommended storage conditions and a high temperature (e.g., 40°C) should be considered, and may be combined with the low temperature cycling study. Storage time should be at least 24 hours under each condition, and containers should be stored under each condition at least five times. The containers should be examined visually for any obvious defects, and tests such as leak rate, weight loss, delivered dose uniformity, fine particle mass, related substances and moisture content should be performed. Any changes from initial results should be assessed for their significance.

Effect of environmental moisture: The effect of environmental moisture on product performance should be investigated during development. For pre-metered products using capsules, special attention should be paid to brittleness of the capsules under various humidity conditions.

Robustness: The product performance should be investigated under conditions to simulate use by patients. This includes activating the delivery device at the frequency indicated in the instructions for use. Carrying the delivery device between use and simulation of dropping the delivery device etc. and the robustness of any lockout mechanism should be considered. Vibrational stability of powder mixtures should be demonstrated, in order to simulate vibrations during transport and use. Significant variations in the delivered dose and/or fine particle mass should be fully discussed in terms of the safety and efficacy of the product.

Delivery device development: The development of the delivery device should be described. Any changes implemented in the design (e.g. change of component materials) and/or manufacturing process of the delivery device (e.g. scale up from single cavity to multiple cavity tooling) during the development of the product should be discussed in terms of the impact on the product performance characteristics (e.g. delivered dose, fine particle mass, etc.) If prototype delivery devices were used in clinical studies, appropriate data should be provided to demonstrate the equivalence of the prototype(s) with the product intended for marketing.

For device-metered dry powder inhalers, safeguards to prevent inadvertent multiple dose metering (and subsequent inhalation by the patient) should be demonstrated. For breath-activated delivery

devices, data should be provided to demonstrate that all target patient groups are capable of triggering the delivery device. This could be evaluated as part of the clinical programme during patient handling studies. The triggering mechanism should be well characterised as part of the delivery device development programme. For device-metered dry powder inhalers each unit should have a counter or other fill indicator to give the patient some indication of when the number of actuations stated on the label has been delivered. Inclusion of dose counters is also encouraged for other multiple dose products.

Preservative effectiveness / efficacy: For products containing a preservative, a study should be conducted to demonstrate the effectiveness / efficacy of the preservative.

Compatibility: If the product is to be diluted prior to administration, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples, and should cover the duration of storage of the diluted product indicated in the labelling. Where the labelling specifies co-administration with other drugs, compatibility should drug as well as the co-administered drug. Parameters such as precipitation, pH, droplet size distribution, output rate and total drug output should be tested, and differences from the original product should be assessed for their significance.

With the implementation of Quality by design (QbD) in countries like US, Europe and Japan, Research based companies would be looking at the possibility of using this in the development of OINDP's. However, using QbD concept in the development and manufacture of OINDP's presents a unique challenge. QbD is significantly more complex for inhaled products than for other dosage forms because, for example, product performance is a function of both device and formulation. A patient's operating technique may influence the received dose. Product manufacture and use is influenced by environmental conditions. There is a lack of relevant real time analytical tools. These issues means that the adopting of QbD for OINDP's may be relatively slow and may also depend on the development of new measurement techniques.

Reference:

EMA-2006 Guideline on the pharmaceutical quality of Inhalation and Nasal Products.; Guidance for Industry Health Canada 2006.

Novel drug delivery systems : A Microemulsion based approach

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Now a days, pharmaceutical research is aimed at developing suitable drug delivery systems which will efficiently deliver the drug to fulfill the therapeutic needs of the patient. The development of novel drug delivery should meet/on par with the development of new chemical entities, where majority of the molecules discovered were hydrophobic in nature. In the thrust of developing new delivery systems, microemulsions gained a prominence in the effective delivery of the hydrophobic drugs. Microemulsions are thermodynamically stable, transparent, isotropic, low-viscosity colloidal dispersions consisting of oil and water stabilized by an interfacial film consisting of surfactant/co-surfactant and newtonian non-viscous liquid in nature. They are capable of solubilizing both hydrophilic and lipophilic ingredients with relatively higher capacities. Recently drug delivery systems involving liposomes, emulsions/microemulsions, solid lipid nanoparticles were proven promising in the delivery of poorly soluble/lipophilic compounds. Microemulsions were found to be nanostructured vehicles which can be potentially used for the delivery of the drugs through oral, parenteral and transdermal routes. In the present review microemulsion formulation components and their applications in various delivery systems i.e. oral, parenteral and transdermal are discussed briefly.

Introduction

A number of poorly water-soluble drug compounds are constantly increasing as a consequence of modern drug discovery techniques like advances in *in vitro* screening methods, the introduction of combinatorial chemistry, etc and to date, more than 40% of new chemical entities are lipophilic and exhibit poor water solubility¹. Indeed, a poor aqueous soluble active ingredient shows superior solubility in lipid phase than aqueous phase. In this regard natural and synthetic lipids have generated much commercial interest for delivering the poor water soluble drugs efficiently. In terms of lipophilicity, generally drugs which are having log P>3 are suitable candidates for the microemulsion based drug delivery systems. Drug delivery systems like solutions, suspensions, emulsions, self-emulsifying systems, liposomes, solid lipid nanoparticles and microemulsions can be formulated by using lipids. Microemulsions are solution-like systems with an inner structure of nanodroplets stabilized by a set of surfactants and co-surfactants².

Microemulsions offer various advantages like thermodynamic stability, ability to entrap hydrophilic, hydrophobic therapeutic agents. These systems show the improved oral bioavailability due to enhanced solubility and permeability of the drug in the entire area of the gastro-intestinal

tract. Enhanced dermal transport was observed with these delivery systems in the transdermal drug delivery due to lipophilicity and improved permeation rate in presence of surfactants. In parenteral drug delivery the microemulsion technology has taken edge over the co-solvent approach, where the former technology involves the nano size droplets which make them more compatible to administer, while the later is having the drawbacks of toxicity for example Taxol[®]. Besides these obvious advantages, also involves less number of unit operations in the formulation development, which is more convenient for the manufacturers in terms of economy.

Microemulsification technology is mainly influenced by various factors such as nature and concentration of the oil, surfactant (required HLB value to emulsify oil and type of emulsion i.e. O/W or W/O), co-surfactant, aqueous phase, oil/surfactant and surfactant/co-surfactant ratio, temperature, and physicochemical properties of the API. As the surfactants are toxic in nature, excipient acceptability by regulatory authority should be considered for the desired route of administration. It is advisable to use excipients which are included in "Generally Recognized As Safe (GRAS)", this is very much significant in developing formulations for parenteral delivery. Final drug product

can be dispensed in the form of Liquid-filled gelatin capsules, Solution (e.g.: Neoral[®] for cyclosporine), and as hydrogels.

Formulation Components:

Selection of suitable excipients plays a significant role in formulating successful product to achieve maximum drug loading with desirable pharmacokinetic profile.

Oil phase:

As a preformulation study, solubility of drug substance in different oils should be performed to select the appropriate oil phase in order to achieve maximum drug loading in the formulation. Solubility of drug substance in oil phase is determined by the log P value which is a measure of hydrophobicity of drug substance. The selected oil should be capable to form microemulsion when diluted with aqueous phase. Djekic et al.³ concluded that low molecular volume oils, such as fatty acid esters and triglycerides with medium chain lengths are preferred instead of high molecular volume oils to form microemulsion. A range of oils⁴ (lipophilic liquid vehicles) which are used to formulate microemulsions are given in table 1.

Surfactant / Co-surfactant:

Surfactant/ Co-surfactant are mainly used for reducing interfacial tension almost to zero between oil phase and water phase to form microemulsion. For spontaneous microemulsification of pre-concentrate

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(mixture of oil and surfactant) following aqueous dilution, high surfactant concentrations are required, insufficient amount of surfactant can yield a coarse emulsion with increased tendency for drug precipitation⁵. Surfactants, at higher concentration may cause haemolysis on parenteral administration, causes irritation to the gastrointestinal mucosa and skin. Hence it is advisable to use natural surfactants like phospholipids than synthetic surfactants. Synthetic surfactants are divided into three categories based on their charge i.e. cationic, anionic, and non-ionic. Among these non-ionic surfactants are preferred over ionic surfactants. Polysorbates are known to form complexes with preservatives like methyl paraben and propyl paraben and which may influence properties of microemulsion. Higher concentration of preservatives required to provide adequate preservation when non ionic surfactants are used in formulation. Widely used surfactants are listed in table 2.

Co-surfactants interact with surfactant monolayer at the interface thereby affects their packaging which results in the formation of flexible interfacial layer. The flexible film avoids the formation of liquid crystalline phase which will often form due to rigidity of surfactant film. Majorly in the formulation of microemulsions, an amphiphilic short chain molecule acts as co-surfactants⁶. Examples of co-surfactants are listed out in table 3.

Aqueous Phase:

Generally water is used as an aqueous phase in the formulation of microemulsions. However, to maintain isotonicity with body fluids in parenteral and ocular formulations electrolytes are added provided those additives should not change the phase behaviour of microemulsion. Kawakami et al.⁷ used physiological fluid such as ringer's solution to predict the behavior of microemulsion *in-vivo* as large amount of multivalent cations found in small intestine. pH of the aqueous phase is also important in oral delivery as the formulation will be exposed to gastric fluids of various pH ranges from 1.2 to 6.8.

Applications in Drug Delivery:

The final dosage form should be appropriate for desired route for administration. As these formulations having versatile characteristics from conventional dosage forms in terms of appearance, viscosity, ease of sterilization and preparation which make them ideal drug delivery vehicles. These microemulsions are found to be stable, because the development process was not involving any

high energy inputs, which makes them thermodynamically stable systems.

Oral microemulsions:

Therapeutic efficacy of orally administered drugs is mainly hampered by their poor water solubility. The dissolution rate of such drugs can be extremely low under physiological conditions leading to poor oral bioavailability, nonlinear exposure with increasing dose, exhibits strong food effect where the bioavailability increases due to the solubilizing effects of ingested food and concomitant excretion of bile and high intra and inter subject variability. Drug substances that exhibit high lipophilic properties will be beneficial to dose them in a pre-dissolved state in solubilized form, thereby the food interactions can be minimized and the bioavailability can be enhanced to a great extent⁸.

As these systems are transparent unlike emulsions make them patient compliance at the same time suffer from disadvantages like poor palatability due to their lipidic composition which leads to poor acceptability. Recently these disadvantages were overcome by formulating the anhydrous form of microemulsion/ microemulsion concentrate which is in the form of soft gelatin capsule, these systems forms the microemulsion on contact with the physiological fluids. These systems are also described as self microemulsifying drug delivery systems (SMEDDS).

In the microemulsion systems, lipid components such as glyceryl monooleate and long-chain triglycerides have been shown to promote the lymphatic absorption of the therapeutic agents from gastrointestinal tract which prevent the first-pass metabolism of the drugs⁹. Similarly non-ionic surfactants such as polysorbate 20, polysorbate 80, acacia, solutol HL 15, vitamin E TPGS and cremophor EL shows p-gp inhibitor resulting in increase in oral absorption¹⁰.

Oral delivery of proteins/peptide drugs usually results in poor bioavailability due to low permeation of the protein, because of its large size, hydrophilicity and extensive degradation in the harsh environment of the gastro-intestinal tract¹¹. FDA approval of microemulsion concentrate in the form soft gelatin capsule as well as oral solution with trade name NEORAL[®] for cyclosporine A, a peptide drug to improve the oral bio-availability, confirms the potential of microemulsion to deliver the hydrophobic compounds, which is commercially exploited.

Absorption of drug substance from microemulsion is influenced by several factors such as particle size, partition coefficient of the drug between the two immiscible phases, the presence of the drug in the interface, site or path of absorption, microemulsion components that can act as absorption enhancers and drug solubility in microemulsion components².

Cui et. al. formulated new self microemulsifying drug delivery system to improve the solubility and oral absorption for curcumin, is a poorly water-soluble drug¹². The optimal formulation of SMEDDS was comprised of 57.5% surfactant (emulsifier OP: cremophor EL = 1:1), 30.0% co-surfactant (PEG 400) and 12.5% oil (ethyl oleate). The results of oral absorption experiment in mice showed that SMEDDS could significantly increase the oral absorption of curcumin compared with its suspension.

Patel et al.¹³ formulated stable SMEDDS and tested for microemulsifying properties like clarity, precipitation and particle size distribution for fenofibrate. Phase diagrams are used for screening and development of formulations. The optimized formulation composed of labrafac CM10, tween 80 and polyethylene glycol 400 subjected for *in vitro* dissolution and pharmacodynamic studies. SMEDDS showed complete release in 15 minutes as compared with the pure drug, which showed a limited dissolution rate. The pharmacodynamic evaluation of SMEDDS formulation significantly reduced serum lipid levels in phases I and II of the Triton test, as compared with plain fenofibrate. Thus, the study confirmed that the SMEDDS formulation can be used as a possible alternative to traditional oral formulations of fenofibrate to improve its bioavailability.

Self-nanoemulsifying drug delivery systems (SNEDDS) were developed for cefpodoxime proxetil (CFP), poorly bioavailable, high dose antibiotic having pH dependent solubility. Solubility of CFP in oily phases and surfactants was determined to identify components of SNEDDS. Ternary phase diagrams were constructed to identify area of nanoemulsification for the selected systems. Date et al. succeeded in formulating SNEDDS of CFP having mean globule size of 170nm, which was not affected by the pH of dilution medium and SNEDDS released CFP completely within 20 min irrespective of the pH of dissolution medium¹⁴.

Mahmoud et al. succeeded in formulating solid SNEDDS in the form of

tablets as a conventional dosage form, composed of HCO-40, transcutol HP and medium-chain triglyceride. Essential properties of the prepared systems of carvedilol solubility and self-emulsification time were determined. In order to optimize SNEDDS, formulation dispersion-drug precipitation test was performed in the absence and presence of cellulosic polymers. Furthermore, SNEDDS was loaded onto liquisolid powders and carvedilol showed acceptable solubility in the selected excipients. It also demonstrated improvement in the stability upon dilution with aqueous media in the presence of cellulosic polymers. Use of granulated silicon dioxide improved the physical properties of liquisolid powders containing SNEDDS. It improved the compressibility of the selected powders and the tested SNEDDS showed marked P-gp inhibition activity¹⁵.

Transdermal Microemulsions:

The main limitation lies in the barrier function of the skin, which is considered one of the most impermeable epithelia of the human body to exogenous substances. Therefore, the major challenge for topical formulations today is to provide a sufficient increase for the drug penetration into the skin. Solubility of the drug in the microemulsion system and the constituents of system i.e. surfactants act as penetration enhancers favors drug delivery to the skin. However the limitation involves irritancy of surfactants at administration site¹⁶. Very low surface tension in conjunction with enormous increase in the interfacial area due to nanosized droplets of the microemulsion influences the drug permeation across the skin. As it is difficult to apply & maintain low viscous formulation on to the skin, different hydrogel matrices such as carbomer 940, xanthan gum and carrageenan have been used to increase the viscosity of microemulsion for topical application¹⁷.

Shishu et al. formulated microemulsion based formulations for topical delivery of acyclovir. Microemulsions were developed using isopropyl myristate/Captex 355/Labrafac as an oil phase, Tween 20 as surfactant, Span 20 as co-surfactant, and water/dimethylsulfoxide (1:3) as an aqueous phase. Transcutol, eucalyptus oil, and peppermint oil were used as permeation enhancers. *In vitro* permeation studies through mice skin were performed using Franz diffusion cells and concluded that formulation containing 2.5% transcutol as the penetration enhancer showed 1.7-fold enhancement in flux and permeation

coefficient as compared to marketed cream and ointment formulation¹⁸. Chen et al. formulated stable microemulsion based hydrogel formulation for topical delivery of ibuprofen. Ethyl oleate (EO) was used as the oil phase, due to a good solubilizing capacity and excellent skin permeation rate. The pseudo-ternary phase diagrams for microemulsion regions were constructed using ethyl oleate as the oil, tween 80 as the surfactant, propylene glycol as the co-surfactant. Various microemulsion formulations were prepared and evaluated for the *in vitro* release through porcine skin using Franz diffusion cells. Results showed that microemulsions increased the permeation rate of ibuprofen 5.72-30.0 times over the saturated solution. Xanthan gum as a gel matrix was used to construct the microemulsion-based hydrogel for improving the viscosity of microemulsion for topical administration¹⁷.

Parenteral Microemulsions:

Hydrophobic drug delivery via parenteral route is a very challenging task. Most frequently hydrophobic drugs are formulated using co-solvents, such as ethanol, propylene glycol and polyethylene glycol 400. Co-solvent based systems often lead to precipitation of the drug on dilution in several cases as reported for paclitaxel and tacrolimus⁶. Propofol is a potent lipophilic anesthetic that was initially formulated in cremophor EL for human use. Because of the occurrence of cremophor EL anaphylaxis and improvements in the quality of lipid emulsions, it was ultimately brought to market as 1% propofol formulated in 10% soybean oil emulsion. Drawbacks to such formulations include inherent emulsion instability, pain at the injection site, need for antimicrobial agents to prevent sepsis¹⁹. Osmolarity, surfactant toxicity, *in vitro* haemolytic activity should be carefully evaluated for these formulations. So, microemulsions can be considered as one of the alternative dosage form to deliver hydrophobic drugs via parenteral route.

The potential of the microemulsions to improve the parenteral delivery of propofol was evaluated by Date et al.²⁰ Formulated propofol microemulsions using pseudo-ternary phase diagrams were evaluated for globule size, physical and chemical stability, osmolarity, *in vitro* hemolysis, pain caused by injection using rat paw-lick test and *in vivo* anesthetic activity. The microemulsions exhibited globule size less than 25 nm and demonstrated good physical and chemical stability. Propofol microemulsions were slightly hypertonic and resulted in less than

1% hemolysis after 2h of storage with human blood at 37°C. Propofol microemulsions were significantly less painful as compared to the marketed propofol formulation and anesthetic activity was similar to the marketed propofol formulation indicating that they do not compromise the pharmacological action of propofol. The formulated product was found to be stable for 3 months under storage conditions of 5 ± 3°C.

Kale et al. developed lorazepam (LZM) microemulsions as an alternative to the conventional co-solvent based formulation. Initially the solubility of LZM in various oils and Tween 80 was determined. Capmul MCM demonstrated highest solubilizing potential for LZM and was used as an oily phase. LZM microemulsions were compatible with parenteral dilution fluids and exhibited mean globule size less than 200 nm. The *in vitro* hemolysis studies indicated that microemulsions were well tolerated by erythrocytes. The LZM microemulsions containing amino acids exhibited good physical and chemical stability when subjected to refrigeration for 6 months²¹.

Reddy et al. studied the influence of pegylation of parenteral emulsion (PE) on their long circulating property²². Etoposide encapsulated parenteral emulsion (EPE) was prepared using soybean oil, egg lecithin and cholesterol. Etoposide encapsulated long circulating parenteral emulsion (PEG-EPE) was prepared using PEG (2000)-DSPE as a stealth agent. The effect of monovalent and divalent electrolytes on the stability of etoposide was assessed by measuring the fixed aqueous layer thickness (FALT) and flocculation rate. Pharmacokinetics and tissue distribution pattern of PE following i.v. (bolus) were assessed in Wistar rats and Swiss albino mice. Results showed that FALT of PEG-EPE was larger than that of EPE. The increased circulation time of PEG-EPE (0.3%) after intravenous injection to rats confirms the presence of FALT around globules. PEG-EPE showed improved pharmacokinetic parameters with 5.5 times higher AUC than etoposide commercial formulation (ETP). Tissue distribution results show that etoposide levels in all tissues except in brain and heart were lower in case of PEG-EPE than ETP. The improved activity of PEG-EPE is due to enhanced permeability and retention effect (EPR).

Rossi et al. attempted to correlate the surface properties of the emulsions with

blood residence time and accumulation into neoplastic tissues by passive targeting²³. To correlate oil-in-water emulsions (100-120 nm in diameter) prepared and investigated the effect of phospholipid and sphingolipid emulsifiers, hydrogenated soybean phosphatidylcholine (HSPC) and egg sphingomyelin (ESM), in combination with polysorbate 80 (PS-80) and 1, 2-distearoyl -sn- glycerol - 3 phosphatidylethanolamine (DSPE)-PEG lipids of various PEG chain lengths and structures in prolonging circulation time and enhancing accumulation into B16 melanoma or C26 colon adenocarcinoma. The relationship between amphiphile molecular packing at the air/water interface on emulsion stability upon dilution in albumin and circulation longevity *in vivo* was also explored for non-PEGylated emulsions. PEGylation of the droplet surface with 10-15 mol% of DSPE-PEG 2000 or 5000 enhanced the circulation time of the emulsions, however, accumulation was only observed in the C26 tumor model. The tighter molecular packing observed with ESM/PS-80 monolayers at the air/water interface compared to HSPC/PS-80 correlated with improved emulsion stability *in vitro*, however, enhanced circulation time *in vivo* was not observed. A better understanding of the relationships between composition and performance will result in improved emulsion-based drug delivery vehicles for cancer therapy.

Conclusion:

Certainly, hydrophobic drugs are rising in number as a result of combinatorial chemistry for which suitable drug delivery is an ultimate goal. Microemulsions are one of the best promising delivery systems which are helpful to move hydrophobic compounds for commercial use. Microemulsions can be considered as one of the formulation strategy to deliver hydrophobic drugs efficiently via oral, transdermal and parenteral routes. Microemulsions were proved for the improved oral bioavailability, enhanced permeation of drugs across skin and long circulation in the physiological systems which is very vital to reduce systemic toxicity. However, the major limitation is the toxicity of excipients i.e. surfactant/ co-surfactants. Exploration of safe excipients and evaluation of the toxicity parameters of available excipients may help in further expansion of research in this field.

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S.No	Type of oil	Example
1	Fixed oils	Soybeanoil, Arachis oil, Castor oil, Cottonseed oil, Maize (corn) oil, Olive oil, Sesame oil, Soybean oil, Sunflower oil.
2	Medium-chain triglycerides and related esters	Caprylic/capric triglycerides (Akomed E, Akomed R, Miglyol 810, and Captex 355)
3	Medium-chain triglyceride	Labrafac CC
4	Propylene glycol diester of caprylic/capric acid	Labrafac PG
5	Propylene glycol monolaurate	Lauroglycol FCC
6	Fractionated coconut oil	Miglyol 812
7	Caprylic/capric/diglyceryl succinate	Miglyol 829
8	Medium-chain diesters of propylene glycols	Miglyol 840
10	Medium-chain mono and di-glycerides	Mono and diglycerides of capric/caprylic acid. (Capmul and Imwitor)
11	Fatty acid esters	Ethyl Oleate, Isopropyl myristate, Isopropyl palmitate.

Table 1: Oils used for the formulation of Microemulsions

S.No	Type of surfactant	Example
1	Non-ionic surfactants	Hydrogenated polyoxyl castor oil (Cremophor EL), Polyoxyl-40 hydrogenated castor oil: (Cremophor RH 40) Glyceryl monooleate, Polyoxyethylene(20)sorbitan monolaurate (Tween 20), polyoxyethylene(20)sorbitan monooleate (Tween 80), Sorbitan monolaurate (Span 20), Oleoyl macrogol-8 glycerides (Labrafil M 1944CS) Linoleoyl macrogolglycerides (Labrafil M 2125 CS), PEG-8 caprylic/capric glycerides (Labrasol),
2	Phospholipids	Soybean lecithin, Egg lecithin, Diolelyl phosphatidyl choline, Distearoyl phosphatidyl glycerol, PEGylated phospholipids

Table 2: Widely used surfactants for formulation of Microemulsions

S.No	Type of co-surfactant	Example
1	Short chain alcohols	Ethanol, Isopropanol, n-butanol
2	Alkane diols and triols	Propylene glycol, glycerol
3	Polyethylene glycols	PEG 400, PEG 600
4	Glycol ethers	Transcutol.

Table 3: Co-surfactants for formulation of Microemulsions