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A REVIEW: ORAL FORMULATION DEVELOPMENT

Shruti Gupta*[1] and Anoop Kumar Singh[2]

[1]Research Scholar, S.N. College of Pharmacy, Jaunpur.

[2]Director, S.N. College of Pharmacy, Jaunpur.

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***Corresponding Author**
Shruti Gupta
Research Scholar, S.N.
College of Pharmacy,
Jaunpur.

ABSTRACT

Pharmaceutical formulations must meet a number of criteria depending on how they will be used, whether during the development process or as a finished product. With their unique features, new drug candidates provide the formulation scientist with practical difficulties that must be overcome in order to meet regulatory standards, time constraints, and resource constraints. In an effort to increase the medicine's bioavailability, disguise its taste, trigger a speedy beginning of action, and increase patient compliance, modern drug delivery systems have been used. Orodispersible system is a substitute for the traditional dose form that is being used to overcome all of these problems. Poor water solubility for many therapeutic molecules being developed today is a major obstacle to reaching appropriate The term "nanosizing" refers to the process of reducing active pharmaceutical ingredient (API) particle size to the sub-micron range; the final particle size is typically between 100 and 200 nm. The rate of dissolution of the API improves considerably with decreasing particle size, which may lead to significant improvements in bioavailability. This review covers the fundamentals of nanosizing, the development and characterization of nanoformulations, as well as the actual application of such formulations in vivo.

KEYWORDS: Oral formulation, Pharmaceutical formulations, Active pharmaceutical ingredient, Tablets.

INTRODUCTION

Since the beginning of pharmaceutics, oral delivery has been the most significant mode of administration. This blatant dominance has altered recently as a result of the growth of biopharmaceuticals, which are often injected. Oral formulations, however, are probably going to continue to be important in the future due to their simplicity in administration, good

stability, well-established manufacturing processes, and affordable cost of goods. While the justifications for favouring oral administration are frequently simple and part of the target product profile (TPP), choosing a formulation strategy or a process technology is more challenging. Companies frequently display pronounced variances in their decision-making process for formulating strategies. In addition to strategic considerations (like outsourcing) and corporate traditions, scientific reasons are also crucial. The outcomes of pharmaceutical profiling and biopharmaceutical modelling provide an initial basis for decision-making for new drug candidates.[1]

The strategies and approaches that have been and are still used in product development vary greatly from company to company, and even between project teams within the same organization, due to the complexity of solid dosage forms and the difficulties in applying the basic and applied scientific principles in the pharmaceutical industry. As a result, considerable effort and resources are frequently used without guaranteeing a respectable success rate. The adoption of a rational development strategy with a higher degree of scientific knowledge has, however, become a new philosophy in recent years. This philosophy has been promoted through academic and industrial research, as well as regulatory advice.[2]

The ultimate goal would be to create a pure medicine that exclusively included the natural protein. Only having the native form of a protein in the formulation, however, is impractical because the protein must be isolated from a complex biological mixture that also contains misfolded, denatured, and degraded forms of the same protein. Maintaining the purity of the purified protein during ordinary pharmaceutical manufacturing, storage, handling, and delivery to the patient is also a significant difficulty. This objective may be attained by creating a formulation with complete stability, meaning no physical or chemical alterations to the protein.[3] Since proteins are intricate molecules made up of a variety of reactive chemical groups and delicate three-dimensional structures, it is virtually impossible to identify a set of conditions that will keep every component stable. In general, it is assumed that some degree of physicochemical alterations will take place during storage and handling when developing commercial therapeutic protein formulations.[4]

Ingredient technology and formulation development

The three essential qualities that make surimi seafood useful are colour, flavour, and texture. Color and flavour can be controlled rather easily, but managing texture is more difficult since

the addition of ingredients predominantly impacts the product's textural features nonlinearly. As a result, there are several distinct kinds of textural attributes. The main ingredients used in the formation and modification of the textural properties of surimi seafood are surimi, water, starch, protein boosters, and hydrocolloids. outlined the relationship between the sensory and physical aspects of texture. Human mouths have a "brittle" sensation when a product has a relatively high stiffness in comparison to its cohesion. The structure of brittle foods strongly resists deformation, yet if enough force is applied, the food will crumble before noticeable deformation has occurred. Low stiffness/cohesiveness ratios, however, indicate a "rubbery" composition. The magnitude of the two textural factors together places the textural descriptor on a continuum, from a "mushy" (neither stiff nor rubbery) feeling up to one of toughness.[5] For seafood surimi, the stiffness and cohesiveness of the texture are typically balanced.[6,7]

Oral formulation development

Over the preceding 20 years, the intricacy and specificity of drug-receptor targets have surged. Combinatorial chemistry advances and high throughput screening have made it feasible to create drugs that precisely target these many targets. The structural complexity and solubility of the active medicinal ingredient have increased as a result of these developments, which is unfortunate but not entirely unexpected. Because of this, it's critical to understand and research recent advancements in formulation techniques to improve the solubility of medications that are only weakly water-soluble.[8]

Role of Excipients in the Formulation Development

Liquid Dispersions

Drug delivery and development have continued to be interested in liquid dispersions.[10] It has been determined that the lipid-based delivery systems (LBDS) are "true liquid dispersions for self (micro) emulsification drug delivery systems" (S(M)EDDS)" and that they have been successfully used in the development of lipophilic molecules that are poorly soluble and have 2 logP values. 4. SEDDS and SMEDDS are suitable for those requiring the highest achievable doses and offer an easy scale up for manufacturing these dosages in oral solutions, liquid/semi-solid for soft gel, and/or pellets for hard gel capsules or tablets.[9] Excipients for LBDS come in a wide variety of molecular compositions, structures, and functionalities. These include, but are not limited to, polar and non-polar solubilizers/surfactants that can self-assemble into aggregates in aqueous solutions and maintain the desired concentrations in gastrointestinal (GI) fluids. Most significantly, the critical micelle concentration (CMC)

and/or hydrophilic lipophilic balance (HLB) values of these surface active excipients (natural or synthetic) are used to describe them.[10]

Solid Dispersions

In the industry, solid oral dose formulations (SODF) have been the main emphasis. For highly crystalline, high melting lipophilic pharmaceuticals, the solid dispersions are completely used, and the medications are transformed into a high energy amorphous powder to maximise solubility and bioavailability.[11] Many solid dispersion methods are in the early phases of development, such as Kinetisol®, microwave irradiation, and electrospinning, as well as highly developed (such as hot melt extrusion, spray drying, coprecipitation, melt granulation, and lyophilization).[12–14] The excipients that are essential for a reliable formulation are called enablers. For compatibility and stability prediction of amorphous dispersions, the structure-function characteristics of excipients, interactions with drugs, and their effects on long-term stability and formulation performance are taken into account.[15]

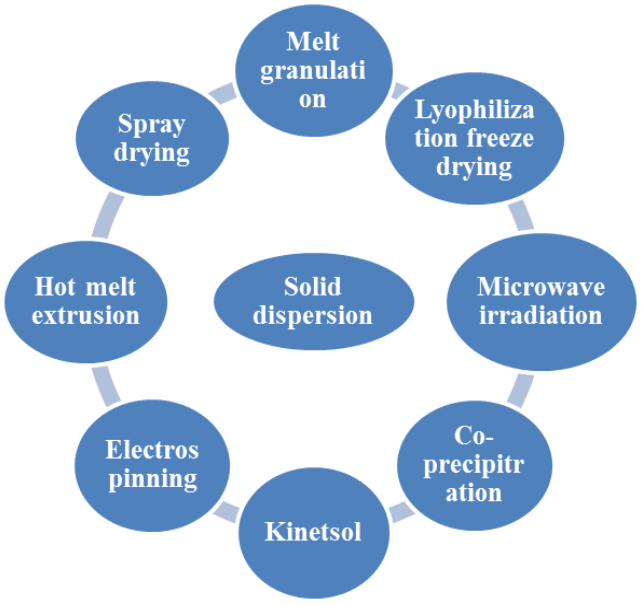

Figure 1: Methods for preparation of solid dispersions.

The purpose of this paper was to study the solubility

creation of formulations for oral administration of medications with restricted water solubility involves permeability interaction. The apparent solubility of the lipophilic drug carbamazepine was evaluated in systems containing different amounts of the co-solvent PEG-400. The related permeability was then evaluated using the PAMPA test and the rat jejunal perfusion model. The thermodynamic activity was maintained at 50% saturation for the

duration of the permeability study. Carbamazepine's solubility was enhanced by PEG-400 in a concentration-dependent manner. The medication carbamazepine showed an increase in apparent solubility and a decrease in intestinal permeability in both the PAMPA and rat perfusion models. Furthermore, we have shown that the membrane-controlled intestinal absorption of carbamazepine virtually plays no functional barrier function in the unstirred water layer. The relationship between permeability and solubility was explained by use of a mass transport research. It was shown that the driving force for membrane permeability was reduced by the lower apparent membrane/aqueous partitioning in the aqueous GI environment. In terms of the relationship between solubility and effective permeability, the model produced excellent quantitative predictions. It has been shown that there is a definite trade-off between increasing solubility and lowering permeability, which must be taken into account when developing oral formulations for lipophilic drugs.[16]

Methodology of oral formulation

Pharmaceutical formulations must meet a number of criteria depending on how they will be used, whether during the development process or as a finished product. With their unique features, new drug candidates provide the formulation scientist with practical difficulties that must be overcome in order to meet regulatory standards, time constraints, and resource constraints. This essay tries to evaluate many approaches in order to choose an appropriate formulation strategy for oral administration. The review is prepared from an industrial standpoint and only small-molecular medicines are taken into consideration. With a focus on poorly soluble compounds, specific cases are first discussed. Following that, the subjects of chemically labile drugs, low-dose compounds, and modified release are reviewed. Due to the extensive breadth of this book, a major emphasis is placed on defining fundamental ideas as well as current developments. A structured product development is one of the several approaches to industrial formulation selection that are studied. Finally, the current subject of a manufacturing categorization system is discussed. Examples for such organised development are intended to offer formulators direction. It can be said that the field of choosing oral formulations is particularly complex because there are numerous opportunities as well as challenges, so industrial scientists must use tailored approaches to create formulations that work.[17]

In a dynamic in vitro lipolysis model, the solubility of progesterone and vitamin D3 in long (LCT), medium (MCT), and short (SCT) chain triglyceride solutions was examined. Rats

were used to study the medicines' absolute oral bioavailability in the studied formulations. After cycloheximide (3 mg/kg)-induced lymphatic transport blockade, the bioavailability of vitamin D3 was also examined.[18]

BCS class IV drugs

BCS class IV medicines, including as amphotericin B, furosemide, acetazolamide, ritonavir, and paclitaxel, have a number of properties that make successful oral and intraoral distribution difficult. Drugs are divided into four groups based on their solubility and permeability properties using the BCS: class I, class II, class III, and class IV. Class I: high solubility-high permeability. Class II: low solubility-high permeability. Class III: high solubility-low permeability. Class IV: low solubility-low permeability. Medicines like phenytoin, glibenclamide, carbamazepine, and ibuprofen that have low solubility but adequate membrane permeability are classified as BCS class II drugs. The dissolving stage is the part of the absorption process for class II medicines that is rate-limiting. The pace and volume of such medications' gastrointestinal tract absorption are greatly influenced by their formulation. To enhance the delivery of BCS class II medicines, many formulation techniques, such as complexation, micronization, crystal modification, etc., have been developed. They are based on methods to either speed up drug dissolving or produce sustained drug solubilization. BCS class IV medications include acetazolamide, furosemide, ritonavir, and amphotericin B (AmB), which are weakly water-soluble and have poor membrane permeability. Due to the restricted membrane permeability, procedures employed for BCS class II medications often accomplish nothing to enhance the absorption of class IV medicines. As a result, returning to the lead optimization stage of drug discovery and altering the structures of class IV drugs to obtain the proper physicochemical properties is the best way to increase their bioavailability. However, the process of finding a novel medicinal agent is difficult, expensive, and time-consuming. The development of a new chemical entity costs US $800–1200 million and takes 10–15 years. In addition, only a small fraction of the millions of studied chemicals are commercially available. Due to the limitations on time, money, labour, and resources, returning a therapeutic molecule to the lead optimization phase is not a viable option. In order to create a successful product for the administration of BCS class IV medicines, correct formulation is crucial. It provides information on the many BCS IV medications and the many challenges they provide to effective oral and peroral administration.[20]

The biopharmaceutics classification system (BCS) was used as a starting point to create an updated categorization system for oral medications. The new method is intended to place more emphasis on the potential for medication development. The new approach took into account intestinal solubility, the compensatory nature of solubility and permeability in the small intestine, and an estimate of the particle size required to overcome dissolution rate limiting absorption. The approach was then verified by comparing with existing research on a variety of test drugs' in vivo performance. Observations on the test compounds supported the revised classification, known as the developability classification system (DCS), demonstrating that it is more valuable than the popular BCS in identifying the elements essential to in vivo performance.[21]

One of the most crucial medications in the currently accepted antiviral therapy is acyclovir, a 2′-deoxyguanosine analogue. Acyclovir has a low oral bioavailability due to its biopharmaceutical characteristics, which limits its therapeutic application. According to this interpretation, the goal of this work was to construct ball milling solid dispersions with the hydrophilic carriers Pluronic F68®, hydroxypropylmethyl cellulose K100M®, and chitosan in order to increase the dissolution rate and intestinal permeability of acyclovir. Through several solid state procedures, solid dispersions were created and thoroughly described. For SD HPMC and SD CTS, the solid state data showed a decline in crystallinity (amorphous phase and defects), as well as the existence of hydrogen bonds. All developed SDs showed an increase in dissolution rates. No negative impacts on the in vitro antiviral activity were also found. The intestinal permeability of acyclovir across Caco-2 cells was dramatically increased by the solid dispersions containing Pluronic F68®. In conclusion, the SDs created in this work have the potential to be solid dosage forms with improved biopharmaceutical characteristics that include acyclovir.[22] Both intercalation products can increase drug dissolution enhancement, according to in vitro release experiments, while MgAl-HTlc-FURO performed better due to its varied physicochemical characteristics. After that, this product underwent a supersaturation experiment, and research on its physical stability showed that FURO's re-crystallization is avoided under storage circumstances because the drug's molecular anions are resistant to hydrolytic assault.[22]

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Combinatorial chemistry, high-throughput screening, and genomics have created a technological platform in the drug development industry today that generates a significant number of novel chemical entities with therapeutic potential each year. The upshot was a shift in the chemical makeup of the new chemical entities toward increased molecular weight and rising lipophilicity, which led to poor water solubility, which principally affected the bioavailability of medications taken orally. Therefore, the medicine's poor water solubility hinders not only the biological application of the drug but also its pharmacological development. This review emphasises the substantial solubility issue, formulation options for BCS/BDDCS, and significance of lipid nanoparticles (LNPs). Additionally, this paper sums up how lipids and lipid formulations behave in the human body, Drugs' lymphatic transport in the human body, difficulties with lipid-based delivery, and the contribution of lipids to increased bioavailability With their noteworthy findings in the study results presented by the many researchers, lipid nanoparticles and BCS class II medications are a good choice for the LNPs formulation. According to the information that is now available, the lipid nanoparticles make this drug delivery method one of the most promising and will provide the formulation scientist with a solution. Additionally, it corresponds with the main goals of sustainable chemistry and green chemistry.[24]

Preclinical testing of drug formulation

Preclinical, clinical, and post-market phases of drug development take time and money. It is theoretically possible to develop a medication in seven years if all the procedures are simple. Drug development often takes more than twelve years. Procedures are strictly regulated for both safety and medicinal efficacy. Most of the compounds being researched that have the potential to be medicines are discarded in the early stages of the research process. Clinical trials are conducted after significant in vitro and animal research. Nevertheless, a lot of drugs are abandoned or fail and are never approved as medicines. The drug not working as well as hoped for, side effects, or lack of financial viability are common causes. The pharmacokinetics, effectiveness, and safety investigations for discovery compounds are made possible by formulation creation for preclinical research, which is a crucial step in the drug discovery and development process. The study's findings offer vital information for selecting the most appropriate medication candidates for human testing and for comprehending how preclinical findings translate into clinical outcomes. The development of phase-appropriate preclinical oral formulations frequently faces several difficulties, such as insufficient exposure because of low solubility. Preclinical development includes all of the processes that occur between the start of human clinical trials and laboratory drug discovery. Preclinical studies can be planned to find the optimum method for scaling up a novel treatment, choose the optimal formulation, identify the route, frequency, and length of exposure, and finally support the planned clinical trial design. Each preclinical development package might have different specifics, yet they all have some characteristics. The pharmacokinetic profile, general safety, and toxicity patterns are defined using rodent and nonrodent mammalian models. The mean residence duration of the medication in the body, which is influenced by its innate absorption, distribution, metabolism, and excretion properties, may be calculated for one or more species. The capacity of a treatment to pass the blood brain barrier may be a crucial consideration for medications used to treat Alzheimer's disease or other brain-targeted disorders. Toxicology and safety studies specify the Therapeutic Index to determine the first beginning dosages in clinical trials and identify possible target organs for harmful effects. Important preclinical safety investigations often require regulatory scrutiny in accordance with international norms like the International Conference on Harmonisation and US Food and Drug Administration (FDA) Good Laboratory Practices. Creating the Clinical Plan and getting the new medicine product ready, together with the related paperwork, to comply with the strict FDA Good Manufacturing Practices regulatory criteria are two preclinical development processes that are ongoing. For investigators looking to progress their

candidacy, a variety of commercial and government contract opportunities are available (s). Government programmes like the National Institutes of Health Rapid Access to Interventional Development Pilot Program and the Small Business Innovative Research and Small Business Technology Transfer Grants offer funding and services to help applicants prepare the preclinical programmes and documentation for their drugs. Preclinical research is increasingly receiving support from private foundations. To make sure that the preclinical development package adequately supports the intended phase I clinical trial, close communication with the FDA is essential, including a meeting to prepare for submission of an Investigational New Drug application.[25]

Type of Dosage Forms

Tablets and capsules are the two most popular presentation kinds for solid oral dose forms. Using a tableting machine, properly prepared mixes or granules are compacted into solid masses known as tablets. There are commonly two types of capsules: (1) hard shell (or twopiece) and (2) soft shell. A capsule contains a dosage of medication encased in a water-soluble shell (one-piece). Hard-shell capsules typically have an empty hole that is filled with a granular substance (although it is also possible to fill them with some semisolids and liquids), and the two shells are then mechanically fastened together. A liquid or semisolid matrix is enclosed by a single-piece outer gelatin shell that is often produced on-site in a soft-shell capsule. Additionally, only the encapsulation of granular material will be discussed in relation to hard-shell capsules. The public is accustomed to tablets and hard-shell capsules because they have both been around for a sizable amount of time. Both dosage forms have some inherent benefits, but regrettably each can also have particular drawbacks.[26]

Tablet formulation and design

Precompression was developed, as was induced die feeding in high-speed and, more recently, ultrahigh-speed presses, automated weight-control systems, the availability of numerous new direct compression materials, and microprocessor control of precompression, compression, ejection forces, as well as upper punch tightness on tablet presses. All of these factors have contributed to the recent rapid change and development in the formulation of solid oral dosage forms, and tablets in particular. Some of the most modern tablet presses use computer-controlled tablet rejection mechanisms. Computer-controlled tablet presses only need to be configured by an operator for the proper tablet weight and thickness (or pressure). The run will thereafter be totally controlled by the computer. A user-supplied product identity

is all that is required to operate another set of tablet presses. The run will thereafter be totally controlled by the computer. In order to generate tablets that meet previously established and computer-memory stored requirements, some tablet presses just require the user to submit a product identification code.[27]

Recently, formulation, design, and manufacturing of tablets have been impacted by new federal rules and principles relating to bioequivalence, bioavailability, and validation. In the past, expensive gold-plated pills were created and sold with little understanding of their pharmacological effects. Pharmaceutical preparations have to meet strict standards for appearance and subsequent dosage form stability. The invention of the friable pill signalled the understanding that solid medications must somehow break down within the body for the patient to benefit from the medication. We now understand that dissolution and disintegration do not guarantee therapeutic action. Meyer et al offered information on 14 nitrofurantoin compounds that were assessed both in vitro and in vivo as only one illustration of this idea. Despite the fact that all tested items satisfied USP XVIII requirements for drug content, disintegration time, and dissolving rate, statistically significant variations in bioavailability were found.[28]

From relatively straightforward immediate-release formulations to intricate extended- or modified-release dosage forms, tablet dosage forms or drug delivery systems are available. Although getting the medication "delivered" to the site of action in a sufficient amount and at the right rate is the most crucial function of a drug delivery system, it must also fulfil a number of other crucial requirements. These include the capacity to be economically mass manufactured in a way that ensures the right amount of medicine in each and every dosage unit and in each batch produced, as well as, to the extent feasible, patient acceptance. They also include physical and chemical stability (reasonable size and shape, taste, color, etc. to encourage patients to take the drug and thus comply with the prescribed dosing regimen).[29]

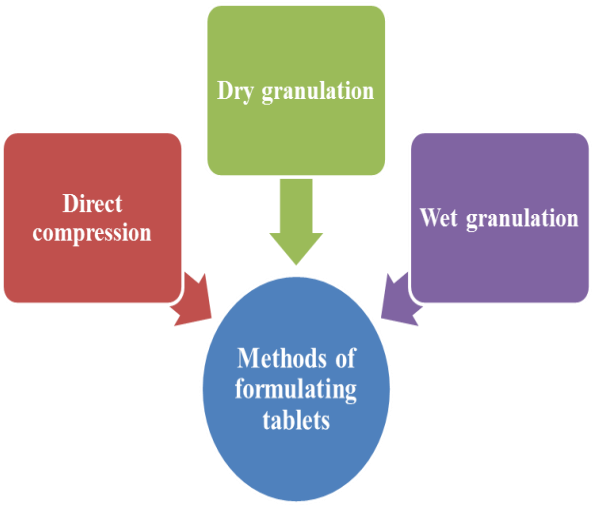

Figure 2: Methods of tablet formulation.

Following are the general design standards for tablets

- The greatest feasible medication absorption from the dose form and availability for the medicine's intended use (ie, immediate or modified release).
- Stability, which takes into account both the stability of the drug material and the overall formulation of the tablet, as well as the pace and amount of drug dissolution from the tablet over a prolonged period of time. It goes without saying that the tablet formulation needs to have a long enough "shelf life" to maintain potency, or the intended drug delivery performance.[30]
- A set of six patients underwent gamma-scintigraphy to evaluate the gastrointestinal transit of a pellet and tablet formulation. Each preparation was labelled with a different radionuclide and distributed concurrently. The transits of the formulations were shown to be highly dependent on dietary intake, and there was a significant correlation between the timing of the transits (gastric emptying, arrival to colon), and the caloric content of the meal eaten just before dosing In a few cases, the pellet system exited the stomach quickly and spread little in the small intestines.

Formulation design of a novel fast-disintegrating tablet

As our society ages, it is normally desired to provide an effective dosage form for senior people. This study examined a new fast-disintegrating tablet as an older patient-friendly dose form. This formulation's benefits include appropriate hardness and simplicity of manufacture using common instruments. The ability to divide saccharides into groups with high and low compressibility allowed for the creation of a material that was suited for swiftly dissolving tablets. By coating and granulating a low-compressibility saccharide with a high one in order

to raise the compressibility of low-compressibility saccharides, a fast-dissolving tablet was made feasible. Another discovery was the existence of the amorphous form of the high-compressibility saccharide used as a binder solution during granulation. The adhesion between the particles and the hardness of the tablet might be increased by purposefully converting the crystal from an amorphous to a crystal form after compression.

The process of conditioning enabled for the appropriate hardness to be attained while maintaining the short disintegration time. Because it can be made using common technology, this rapidly dissolving tablet may be used to administer a range of drugs.[31]

Oral protein delivery has been made difficult for a variety of reasons. However, cutting-edge oral administration methods have been developed that appear promising. The oral peptide 5CNAC, which contains the peptide salmon calcitonin, has the potential to become the first one to be made commercially available in phase III clinical studies for the treatment of osteoporosis or osteoarthritis. The main findings and implications of studies conducted thus far utilising this oral formulation are examined in this paper.[31]

The results include these

- Oral calcitonin 0.8 mg has a short half-life of 9 to 15 minutes, is quickly absorbed, and reaches its peak concentration in 15 to 30 minutes.
- The recommended dose for calcitonin tablets is 0.8 mg.
- Dosing at least 10 minutes before a meal rather than postprandially, combined with 50 mL of water, enhances drug absorption; 5. Biomarker data demonstrate that the 0.8 mg tablet has much superior effectiveness in suppressing bone resorption than the commercial nasal formulation;
- The ideal time to take osteoporosis medicine is in the evening to prevent the circadian peak in bone resorption;
- Both synthetic and recombinant calcitonin oral formulations have similar pharmacokinetic and pharmacological properties. These significant discoveries could aid in the development of novel oral formulations.[32]

Ibuprofen is a widely used prescription and OTC medication. The goal of the project is to produce 200mg Ibuprofen pills using direct compression technology, which is currently thought of as an easy and cost-effective production method. It is thought to be an appropriate method for substances that are both hygroscopic and thermolabile. In order to generate the

greatest, most ideal product, nine different recipes were developed. Diluent (X1), disintegrant (X2), and lubricant (X3) were used as independent variables. Weight variation (Y1), thickness (Y2), length and breadth (Y3), hardness (Y4), friability (Y5), disintegration (Y6), dissolution (Y7), and pharmaceutical assay were all studied as response variables (Y8). All nine formulas' findings were determined to be within acceptable limits and consistent with those listed in official compendia. F-6 was selected as the ideal product due to its high dissolve (99.05%) and assay (100.04%) values. The F-6 capsules had the best excipient ratio and the lowest weight variance of any other formulation. Optimization is a productive method for product development. This is because there is no clear connection between the variables.[33]

Advantage of tablet formulation

Pharmaceuticals with high permeability and poor water solubility make up a sizeable portion of all drugs (BCS class II). This study examines the significant difficulties associated with producing a dry powder appropriate for tableting from a nanosuspension designed to speed up medication absorption. Particle size analysis, dissolution testing, scanning electron microscope imaging, differential scanning calorimetry, and X-ray powder diffraction were used to describe celecoxib, a selective COX-2 inhibitor with limited water solubility. The emulsion-diffusion approach was used to make celecoxib nanosuspensions utilising three different stabilisers (Tween® 80, PVP K-30, and SDS). Spray-dried nanosuspension was combined with microcrystalline cellulose, which was then compressed into tablets. The tablets' tensile strength, porosity, and elastic recovery were all evaluated. The selection of solvent and stabilisers is essential for achieving regulated crystallisation and size as well as for increasing the hydrophobic drug's wettability. The crystalline nano-sized celecoxib alone or in tablets dissolved more quickly and to a greater extent than micronized celecoxib. SEM images showed that the choice of stabilisers had an effect on the nanoparticle shape. Celecoxib nanosuspension stabilised with PVP K-30 and SDS outperformed Tween® 80 due to the dried product adhering and unexpected changes seen on [18DSC curves. Nano-sized celecoxib requires a lot less compaction force to produce tablets with an equivalent tensile strength than micro-sized celecoxib.[33]

- It's simple to deliver tablets.
- It is simple to administer tablets.
- A stronger dose form.
- Maintain dosage age accuracy.

- It is easy to give bitter and nauseating substances in tablet form after properly coating the pills.
- Of all the dose forms, tablets are the smallest and lightest.
- When compared to all other dosage forms, tablet distribution and packaging are the most straightforward and affordable.
- An oral unit dose form is more appropriate for a large-scale manufacture.
- The tablet dosage form is a cost-effective one.[34]

Disadvantages of tablet formulation

- Due to their atmospheric composition and low density, certain drugs are resistant to compression and cannot be made into tablets.
- Different encapsulations or coatings may be required for medications that have disagreeable odours, have a harsh taste, or are sensitive to oxygen or ambient moisture, which might increase the cost of the finished tablets.
- It is challenging to create tablets that offer full drug bioavailability for medications with poor wetting and slow dissolution properties.[35]

Liquid formulations development

When developing an oral liquid dosage form, there are a number of considerations to make, including storage stability and potential interactions, microbiological purity, the properties of the raw materials, such as their solubility and particle size, the dose uniformity and potency, and taste, to name a few. We take care of your specific needs and are there to assist you at every development, scaling-up, and production step. For oral liquid formulations, a variety of products are available, including emulsions, suspensions, solutions, and syrups.[36]

High-quality raw materials that satisfies regulatory criteria

This work develops and characterises self-microemulsifying drug delivery systems (SMEDDS) for liquid and pellet distribution. These SMEDDS increase the water-soluble substance curcumin's solubility, dissolution, and in vivo oral absorption. It was determined how well curcumin dissolved in various media, including oils, surfactants, and co-surfactants. Using pseudo-ternary phase diagrams, the best self-emulsification zone was identified. The optimised SMEDDS used for curcumin formulations in liquid and pellet forms contained 30% mixtures of oils, Labrafac PG, and Capryol 90, and 70% combinations of two surfactants, Cremophor EL and Labrasol (1:1). The curcumin-SMEDDS in liquid and pellet

formulations quickly produced fine oil-in-water microemulsions with particle sizes ranging from 25.8 to 28.8 nm and 29.6-32.8 nm, respectively. Curcumin was released in vitro at a rate and volume about 16 times larger from liquid SMEDDS and SMEDDS pellets than from unformulated curcumin. The plasma concentration-time profiles from pharmacokinetic studies in rats dosed with liquid and pelleted SMEDDS showed 14- and 10-fold greater levels of curcumin absorption, respectively, as compared to curcumin aqueous suspensions. Curcumin-SMEDDS liquid and curcumin-SMEDDS pellets were discovered to be stable for up to 6 months under intermediate and accelerated conditions. These findings demonstrate the promise of the innovative liquid and pellet self-microemulsifying systems for the development of lipophilic medicines with limited oral bioavailability.[37]

A new technique is the liquid formulation of therapeutic proteins. Due to the desire for products that are easy to use in the clinic or that patients may administer themselves, a ready-to-use liquid formulation is appealing. The bulk of modern liquid formulations are composed of the therapeutic protein, water, a buffer, a tonicity modifier, a surfactant, and occasionally a stabiliser. Recent monoclonal antibody formulations often include a pH of 5.7 +/- 0.4, histidine or acetate as a buffer, sucrose or trehalose as a tonicity modifier, and polysorbate 20 or 80 as the surfactant. As long as scholars continue to dispute the excipients' behavioural mechanisms, formulation design will forever remain a black art. Fortunately, a statistical approach like design of experiment is efficient for formula construction when paired with accelerated stability experiments. The development of prefilled syringes and pens has added low viscosity and shear resistance to the characteristics of an effective formulation. To maximise patient compliance for self-administration, it is also ideal to choose formulations that cause minimum pain and tissue damage.[38]

Methods

We describe the development of two distinct families of stable liquid glucagon formulations that "immobilise" the glucagon in solution, possibly by forming micelles and preventing interaction between glucagon molecules, using excipients (LMPC and DDM) that act as surfactants or surfactant-like surfactants. The purpose of this work was to design and evaluate solid and liquid self-emulsifying drug delivery systems (SEDDS) for the medicine atorvastatin, which is not readily soluble. Utilizing solubility experiments, pseudoternary phase diagrams, emulsification studies, and other in vitro testing, the composition of liquid atorvastatin-SEDDS was optimised (thermodynamic stability, droplet size, and zeta potential

analyses). Due to the shortcomings of liquid SEDDS, attempts have been made to develop solid SEDDS (limited dosage form options, poor stability, and mobility during the manufacturing process). Two enhanced liquid formulations, CF3 and OF2, produced solid SEDDS that were adequately dried using the spray drying method. Compared to the liquid SEDDS formulation CF3, which was characterised by reduced turbidity, higher percentage transmittance, and superior self-emulsifying capabilities, solid formulation OF2 exhibited improved solubilization qualities. Overall, the testing revealed that SEEDS might be developed as suitable atorvastatin carriers in both liquid and solid forms. SEDDS and their unique solubilization qualities enable the transport of lipophilic drugs to the gastrointestinal tract in a solubilized state, avoiding dissolution—a problem limiting the absorption rate of BCS Class 2 drugs like atorvastatin.[39]

Advantage of liquid formulation

- Liquid dosage forms are the optimal dosage form for patients, particularly children and the elderly, who have difficulty swallowing pills or capsules (for oral administration).
- They provide positive psychological impacts and a beautiful look.
- Sweetened, coloured, and flavoured carriers can be used to provide drugs with harsh and disagreeable tastes.
- There is more dosing flexibility compared to solid dose forms like pills and capsules. The medication dose may be rapidly and easily altered by measuring a variety of volumes.
- Compared to tablets and capsules, liquid dosage forms are more quickly absorbed when taken orally.
- Liquid dosage forms can be easily used to administer hygroscopic and deliquescent medications that are difficult to administer in solid dosage forms.
- Liquid dosage forms of products like adsorbents and antacids are more effective.
- For some products, such as cough medicines, the liquid dosage form is expected.[40]

Disadvantages of liquid dosage forms

- Compared to solid dosage forms, liquid dosage forms are often more susceptible to chemical degradation.
- They are cumbersome and difficult to store and move because of this.
- The entire dose form is lost if the container is accidentally broken.
- Due to its low stability, a liquid dosage form's shelf life is frequently substantially shorter than that of the comparable solid medication.

- Given that solutions typically provide as favourable substrate for microbial proliferation, a preservative may need to be added.
- Special storage conditions may be needed for liquid dose forms, such as vaccinations.
- A drug's typically unpleasant taste is always more noticeable in solution than in solid form.
- Since the patient must measure the correct volume in order for the dose to be administered, there is a higher chance of dose variability. For patients with vision impairment, arthritis, or those unable to read the numbers on an oral dosing syringe or medicine cup, this can be a serious problem.[40]

Industrial challenges in selecting oral formulations

The pharmaceutical industry's oral formulation tactics have been profoundly influenced by the relatively high attrition rate of trial candidates. A recent analysis of attrition rates in three therapeutic domains, including MRSA (methicillin-resistant Staphylococcus aureus), Alzheimer's Disease (AD), and HCV (hepatitis C virus), compared to the industry average, shows a sombre picture. Efficacy (51%), strategic (29%) and safety (19%) concerns may be further broken down into the attrition data to determine the reasons for termination. To overcome these problems, increased emphasis has been placed on safety and efficacy throughout discovery and the early stages of development.[41] Poor physicochemical and biological properties are frequently cited as the cause of these high attrition rates. However, it must be acknowledged that many commercial pharmaceuticals were produced "at the fringes or even beyond the confines of these suggested drugs' rigorous features," raising worries about tightly enforcing "drug likeness" regulations. For instance, increasing lipophilicity might increase permeability, especially into the target compartment, even while it decreases solubility and improves metabolic clearance. Early phase physicochemical and formulation optimisation has historically been largely disregarded by many organisations (but mostly small, virtual companies) who have purposefully focused on speed to clinical decision making with commensurate minimization of cost expenditure. They often employed basic formulations, such as API powder in bottle (PIB), API powder in capsule (PIC), or extemporaneous compounding techniques, and used the active pharmaceutical ingredient (API) "as is." However, these methods frequently led to non-linear pharmacokinetics, and as a result, insufficient in vivo exposure made it impossible to thoroughly study the clinical pharmacology in preclinical/clinical species. Biopharmaceutical methods have recently

shown to be effective in determining a candidate's "fitness for purpose" and its capacity to provide adequate exposure.[42]

Figure 6: An outline of complexity in drug development.

CONCLUSION

In an industrial setting, developing oral formulations must contend with biopharmaceutical, technological, and time and resource constraints (including scaling up into a manufacturing environment). The TPP, the specific kind of programme, as well as the development stage, which is of special relevance, must all be taken into account while selecting a particular formulation. Poor water solubility, low stability, low dose, or the necessity for regulated drug release are just a few examples of common focal points. Future prospects for the manufacturing categorization system are quite promising. It now focuses on traditional solid oral dose forms, but it has a wider application potential in the future. For enabling formulations like LBFs and ASDs, designing quality into the formulation is very crucial. Specialized CROs and CMOs can fill a gap with the use of particular formulation methodologies. Future formulation selection processes will depend more and more on parallel testing and modelling. The technical risk management of medicinal products will greatly benefit from tailored formulation techniques and a well-structured development process. It could even make it easier for businesses to create drug delivery systems for biopharmaceutically complex medications. The industry has started looking at all methods to expedite development techniques in response to a trend toward more poorly soluble new

chemical entities (NCEs) and rising time and expense in development. As a result, solid dispersions/solutions based on polymers and self-emulsifying delivery systems based on surfactants or lipids have emerged as feasible formulation choices in the pharmaceutical industry. The ketamine lozenge's storage stability was good. Its use in conventional pain therapy was made possible by the excellent bioavailability and repeatability of the compound. During the first pass, there was a substantial norketamine conversion. More study is necessary to determine whether our novel ketamine lozenge formulation is beneficial in treating people with chronic pain conditions. Norketamine, a metabolite that is also an NMDA receptor antagonist, has an important role to be examined because it may significantly affect clinical efficacy. The in vitro lipolysis model is useful for optimising oral lipid formulations even when pre-systemic metabolism in the gut is present. However, if lymphatic transport is a significant pathway for absorption, the data from in vitro lipolysis may not be representative of actual in vivo absorption.

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Conflict of interest

The Authors declare no conflict of interest.

REFERENCE

1. Amidon, G. L., Lennerna¨s, H., Shah, V. P., & Crison, J. R. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical Research, 1995; 12: 413e420.
2. Ashford, M. Introduction to biopharmaceutics. In M. E. Aulton (Ed.), Pharmaceutics: The science of dosage form design (2nd ed., pp. 213e274). Churchill Livingstone, 2002.
3. Dean, D. Packs and packaging. In M. E. Aulton (Ed.), Pharmaceutics: The science of dosage form design (2nd ed., pp. 554e570). Churchill Livingstone, 2002.
4. James M Butler, Jennifer B Dressman, Journal of pharmaceutical sciences, 2010; 99(12): 4940-4954.
5. Filippos Kesisoglou, Santipharp Panmai, Yunhui Wu, Department of Pharmaceutical Research, Merck & Co., Inc., West Point, PA, USA.
6. Rajesh Krishnamurthy, Mark C Manning ,Current pharmaceutical biotechnology, 2002; 3(4): 361-371.

7. Byeong S Chang, Susan Hershenson , Rational design of stable protein formulations, 2002; 1-25.
8. Abhishek Singh, Zelalem Ayenew Worku, Guy Van den Mooter, Expert opinion on drug delivery, 2011; 8(10): 1361-1378.
9. B. Griffin, Advances in lipid-based formulations: Overcoming the challenges of low bioavailability for poorly water soluble drug compounds, Am. Pharm. Rev., March 2012; 41-47.
10. T. Reintjes, "Solubility enhancement with BASF pharma polymers: Solubilizer compendium". BASF SE Pharma Ingredients & Services, Germany, October 2011.
11. B. E. Padden, J. M. Miller, T. Robbins, P. D. Zocharski, L. Prasad, J. K. Spence, J. LaFountaine, "Amorphous solid dispersions as enabling formulation for discovery and early development", Am. Pharma. Rev., 2011; 66-73.
12. J. C. DiNunzio, C. Brough, D. A. Miller, R. O. Williams III, J. W. McGinity, "Applications of KinetiSol® dispersing for the production of plasticizer free amorphous solid dispersions", Eur. J. Pharm. Sci., 2010; 40: 179–187.
13. M. Moneghini, N. De Zordi, D. Solinas, S. Macchiavelli, F. Princivalle, "Characterization of solid dispersions of itraconazole and vitamin E TPGS prepared by microwave technology", Future Med. Chem, 2010; 2: 237–246.
14. S. Ali, N. Langley, D. Djuric, K. Kolter, S. Mirza, "Electrospinning for Solid Dispersions of Poorly Soluble Drugs", CRS 2011; (b) Z. K. Nagy, A. Balogh, B. Vajna, A. Farkas, G. Patyi, A. Kramarics, G. Marosi, " Comparison of electrospun and extruded Soluplus® - based solid dosage forms of improved dissolution", J. Pharm. Sci., 2011; 1-14. (DOI 10.1002/jps.22731)
15. K. C. Waterman, "Accelerated stability assessment program (ASAP): Using science to set shelf life", Pharm. Outsourcing, 2012; 40-46.
16. Avital Beig, Jonathan M Miller, Arik Dahan, European journal of pharmaceutics and biopharmaceutics, 2012; 81(2): 386-391.
17. Martin Kuentz, Rene Holm, David P Elder, European Journal of Pharmaceutical Sciences, 2016; 87: 136-163.
18. Arik Dahan, Amnon Hoffman, Pharmaceutical research, 2006; 23(9): 2165-2174.
19. G.L. Amidon, H. Lennernäs, V.P. Shah, J.R. Crison, A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharmaceutical research, 1995; 12: 413-420.

20. C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Advanced drug delivery reviews, 2012; 64: 4-17.
21. James M Butler, Jennifer B Dressman, Journal of pharmaceutical sciences, 2010; 99(12): 4940-4954.
22. Taylor M, Gerriets V. Acyclovir.
23. Pollier J, Goossens A (May). "Oleanolic acid". *Phytochemistry*, 2012; **77**: 10–15.
24. Rohan Ghadi, Neha Dand , Journal of Controlled Release, 2017; 248: 71-95.
25. Shah, S. M., Jain, A. S., Kaushik, R., Nagarsenker, M. S., & Nerurkar, M. J. Preclinical formulations: insight, strategies, and practical considerations. *AAPS PharmSciTech*, 2014; *15*(5): 1307–1323.
26. Hutchison, K., & Ferdinando, J. Soft gelatin capsules. In M. E. Aulton (Ed.), Pharmaceutics: The science of dosage form design (2nd ed., pp. 461e472). Churchill Livingstone, 2002.
27. Bejugam, N. K., Mutyam, S. K., & Shankar, G. N. Tablet formulation of an active pharmaceutical ingredient with a sticking and filming problem: direct compression and dry granulation evaluations. *Drug development and industrial pharmacy*, 2015; *41*(2): 333–341.
28. Garnet E Peck, George J Baley, Vincent E McCurdy, Gilbert S Banker ,Pharmaceutical dosage forms. Marcel Dekker, New York, 1989; 75-130.
29. Parmar, J. & Rane, Manish. Tablet formulation design and manufacture: Oral immediate release application. Pharma Times, 2009; 41: 21-29.
30. Larry L Augsburger, Mark J Zellhofer, J Swarbick, JC Boylan, Encyclopedia of Pharmaceutical Technology 3, 2007.
31. Takao Mizumoto, Yoshinori Masuda, Takeshi Yamamoto, Estuo Yonemochi, Katsuhide Terada, International journal of Pharmaceutics, 2005; 306(1-2): 83-90.
32. MA Karsdal, K Henriksen, AC Bay-Jensen, B Molloy, M Arnold, MR John, I Byrjalsen, M Azria, BJ Riis, P Qvist, C Christiansen , The Journal of Clinical Pharmacology, 2011; 51(4): 460-471.
33. Rabia Bushra, Muhammad Harris Shoaib, Nousheen Aslam, Durriya Hashmat, M Rehman , Pak. J. Pharm. Sci., 2008; 21(2): 113-120.
34. Andrej Dolenc, Julijana Kristl, Saša Baumgartner, Odon Planinšek, International journal of pharmaceutics, 2009; 376(1-2): 204-212.

35. Tho I. Smeltetabletter--fordeler og ulemper [Orally disintegrating tablets--advantages and drawbacks]. *Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke*, 2012; *132*(4): 424–425.
36. Uchiyama S. Liquid formulation for antibody drugs. *Biochimica et biophysica acta*, 2014; *1844*(11): 2041–2052.
37. Saipin Setthacheewakul, Sirima Mahattanadul, Narubodee Phadoongsombut, Wiwat Pichayakorn, Ruedeekorn Wiwattanapatapee, European Journal of Pharmaceutics and Biopharmaceutics, 2010; 76(3): 475-485.
38. Robert J Falconer, Biotechnology advances, 37(7): 107412, 2019ts.
39. De Saldanha Simon, E., Wingert, N. R., Gobetti, C., Primieri, G. B., Ayres, M. V., de Almeida, S. H. O., Volpato, N. M., & Steppe, M. Development, Quality by Design-Based Optimization, and Stability Assessment of Oral Liquid Formulations Containing Baclofen for Hospital Use. *AAPS PharmSciTech*, 2022; *23*(8): 301.
40. Bye, J. W., Platts, L., & Falconer, R. J. Biopharmaceutical liquid formulation: a review of the science of protein stability and solubility in aqueous environments. *Biotechnology letters*, 2014; *36*(5): 869–875.
41. Amidon, G., Lennernas, H., Shah, V., Crison, J., 1995. A theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res., 12(3): 413–420.
42. Becker, D., Zhang, J., Heimback, T., Penland, R.C., Wanke, C., Shimizu, J., Kulmatycki, K., Novel orally swallowable intellicap® device to quantify regional drug absorption in human GI tract using diltiazem as model drug. AAPS Pharm. Sci. Tech., 2014; 15: 1490–1497.