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Lipid-based oral multiparticulate formulations – advantages, technological advances and industrial applications

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Introduction: Lipid-based formulations have emerged as potential dosage forms to harvest effectively the therapeutic benefits of existing lipophilic molecules and new chemical entities. Compared with existing excipients, lipids by virtue of their unique physicochemical properties and resemblance to *in vivo* components demonstrate the extra advantage of improving the bioavailability of lipophilic and highly metabolizable drugs. Moreover, if used as the major excipient, lipids can reduce the required dose and even the toxicity of drugs with poor aqueous solubility.

Areas covered: This review deals with the importance of multiparticulate systems in drug delivery, the therapeutic and manufacturing advantages of lipids as excipients, and the technological advances made so far in utilizing lipids for multiparticulate dosage forms, with emphasis on their application and success on an industrial scale. Lipids are being widely formulated into different multiparticulate dosage forms using innovative modifications of conventional equipment with relative ease, using methods such as melt-granulation, adsorption on solid support, spray-cooling, melt-extrusion/spheronization, freeze-pelletization, pastillation, and so on.

Expert opinion: There is still a need to design new simple dosage forms and to upgrade existing manufacturing technology, in order to open up new avenues in drug delivery, for preparing patent non-infringing formulations of existing drug products, and to help patients receive treatment at an affordable cost.

Keywords: drug delivery, formulation technology, lipid, liposomes, pastillation, solid lipid nanoparticles, solid lipid pellets, solid self-emulsifying drug delivery systems

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1. Introduction

Drug delivery using lipid-based formulations is one of the emerging strategies to design pharmaceutical dosage forms with improved therapeutic benefits. In recent times, many new chemical entities have been designed based on the structure of their target receptors using combinatorial chemistry and high-throughput screening, which usually results in the discovery of very large molecules with greater degree of lipophilicity. Their poor aqueous solubility leads to poor solubilization in gastrointestinal fluid, low and variable bioavailability and poor *in vitro*/*in vivo* correlation [1]. Though such lipophilic drugs possess great therapeutic advantage, they pose a great challenge for the formulation scientists in their effective delivery. To overcome these issues, lipid-based formulations are now considered as a valuable alternative [2-5]. These formulations have gained popularity because of the unique physicochemical properties of the lipidic excipients and their resemblance to the *in vivo* components, which help to enhance the *in vivo* solubility and thus bioavailability of hydrophobic

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Article highlights.

- Multiparticulate formulations are flexible to design, have good flowability, high physical integrity and strength, low friability, narrow particle size distribution, superior quality for coating application, uniform packing characteristics and are therapeutically superior to conventional single-unit dosage forms.
- Lipid-based formulations improve the oral bioavailability of drugs with poor aqueous solubility.
- Recent technological approaches indicate that liposomes can be manufactured commercially for the development of oral vaccines and other varieties of macromolecular drugs in the near future.
- The development of solid lipid nanoparticles is still in its infancy as it has not been able to reach patients owing to several manufacturing and regulatory issues on the industrial scale.
- Recently developed microparticles/pellets of the self-emulsifying drug delivery system have improved the handling of the formulations.
- Freeze-pelletization and pastillation techniques are new techniques for the fabrication of new and simple lipid-based dosage forms that can open alternatives and new avenues in the field of drug delivery for preparing formulations that do not infringe patents of existing drug products and help patients to receive the treatment at affordable cost.

This box summarizes key points contained in the article.

drugs. The process of digestion and absorption that the lipids undergo in the gastrointestinal tract significantly enhances uptake of associated drugs into the lymphatic system, which helps to bypass the liver and drain them into the systemic circulation by means of the thoracic lymph duct [6].

Lipids such as fatty acids, triglycerides, vegetable oils and their derivatives, used for developing multiparticulate dosage forms, may be available in solid, semi-solid or liquid state. The solid lipids with high melting point (above body temperature) can be directly converted into solid dosage forms, whereas the semi-solid or the liquid lipids may be converted into multiparticulate forms by the process of adsorption on suitable pharmaceutical additives. The process of conversion of liquid into solid dosage forms is advantageous in terms of handling, patient compliance, accurate dosing as well as for improving shelf life of the product. At present, lipids are being widely used for the preparation of different formulations by innovative adaptations and modifications of conventional equipment with relative ease and process simplicity, using methods such as melt-granulation, adsorption on solid support, spray-cooling, melt-extrusion/spheronization, and so on. These techniques facilitate dramatic improvement of the flow properties of the bulk lipids by transforming them into solid particles of definite dimension (powders, granules or pellets), which could subsequently be filled into capsules, sachets or even compressed into dispersible tablets. This review deals with the importance of multiparticulate systems in drug delivery, therapeutic and manufacturing advantages of lipids as drug carriers, and technological advances made so far in utilizing lipids as carriers for the development of multiparticulate dosage forms with particular emphasis on the application and success of such techniques on an industrial scale.

2. Multiparticulate systems and their benefits

A multiparticulate system consists of multiple mini drug depots or drug release units in the form of either a matrix or a reservoir. The term 'multiparticulate' is not restricted to the size of the dosage form; rather, it has been treated in a broader sense where a single administrable dose of drug is distributed uniformly into several smaller units of any defined uniform size and dimension ranging from the nano- to milli-scale. They are generally termed nanoparticles, microparticles, microcapsules, pellets, minitablets and even granules, which can be administered in a single dose by filling them into capsules or sachets (in the case of high dose), or even by compressing them into tablets, preferably a dispersible type, such that the property of each individual particle is retained on disintegration in the gastrointestinal tract [7-9]. They can be manufactured by the agglomeration of fine powders or granules of the drug substance and excipients using appropriate processing technology and equipment. The present pharmaceutical technology has already realized the tremendous potential of this system in terms of its flexibility in design, ease of product development, good 'flowability' resulting from uniform size and spherical shape, high physical integrity of spherical agglomerates, high strength, low friability, narrow particle size distribution, superior quality for coating application, uniform packing characteristics and therapeutic benefits that it offers as compared with the conventional single-unit dosage form [7,10,11]. The greatest advantage of multiparticulate systems is that they can easily be divided into the desired dosage units without any formulation or process change and without any significant effect on the relative percentage drug release profile. The release of drug from any modified release dosage form of multiple strengths changes as a function of its surface area. As in the case of matrix-sustained release tablets, the change in the surface area with change in shape of the tablet is not usually proportional to its dosage strength, which results in dissimilar drug release profiles. Whereas in the case of a multiparticulate system, the number of individual particles increases or decreases with the dose of drug; therefore, the surface area of these dosage forms changes proportionately with the dosage strength, which keeps the drug release profile similar for all the strengths. This eases the process of scale-up and scale-down. It also reduces the extra time and cost incurred in carrying out bioequivalence studies for all other strengths as the bioequivalence report of the highest strength and *in vitro* dissolution profiles of all strengths can be used to claim bioequivalence study waiver for the lower strengths [12]. Moreover, they are also useful in delivering

incompatible drugs together or in administering drugs at different release rates (in pulses) in the gastrointestinal tract. When administered orally, they generally disperse uniformly in the gastrointestinal tract, maximize absorption, minimize localized side effects, reduce intra- and inter-subject variability and lower the risk of side effects by preventing dose dumping [13]. A multiple unit system, by virtue of its small size, can also offer added advantages of prolonged gastrointestinal residence and shorter absorption lag-time [14,15]. Moreover, multiparticulates of size above the nano range can be manufactured with higher drug loads, narrow particle size distribution, spherical shape, good flow properties and low friability [16]. In addition, pellets with similar density and particle size show a lesser tendency to segregation during tableting, which decreases problems such as weight variation and content uniformity, especially for potent drugs [17].

3. Therapeutic advantages of lipids as drug carriers

Lipid-based formulations have frequently been used to improve the bioavailability of drugs. The presence of lipids in the gastrointestinal tract mimics a more or less fed state, which stimulates the secretion of bile salts. The presence of bile salts causes emulsification of the sparingly soluble drug in the gastrointestinal fluid and thus enhances its *in vivo* solubility. This in turn increases the absorption process of the solubilized molecules, which inevitably results in increased oral bioavailability. As drugs from these formulations are preferably routed into the systemic circulation through the lymphatic system, the bioavailability of drug prone to high hepatic metabolism may be enhanced by lipid-based dosage forms. A detailed discussion about *in vivo* processing of lipids in formulations, which improves the availability of poorly soluble drugs in the systemic circulation, is available in the literature [2].

Lipids provide adequate protection to certain sensitive actives from the gastric or environmental conditions owing to their stability at varying pH and moisture levels. They are well established in terms of safety in humans because of their non-cytotoxic and biodegradable nature. The presence of food in the gastrointestinal tract has a minimal effect on these formulations and does not cause any dose dumping when used in controlled release formulations [18]. At present, the number of applications for lipid-based formulations has expanded as the nature and type of active drugs under investigation has become more complex. In such cases, lipid-based formulations may help to shield active ingredients from biological transformation or degradation and thus improve their potency. The solid lipids that have a melting point much higher than body temperature, probably due to their physical state, have an added advantage of maintaining their structural integrity and, therefore, resist *in vivo* action of enzymes for a sufficient period of time. In the case of multiparticulate systems, the rate of enzymatic degradation has been found to increase with decreasing size of the lipid particles as lipase enzyme acts by adsorbing on the particle surface [19]. Along with enzymatic resistance, lipids provide a hydrophobic environment to retard the release of the loaded drug and, thereby, provide a controlled drug release. These properties of lipids have been utilized widely in designing sustained release beads, tablets, suspensions, implants and microcapsules. Moreover, the relatively low density and extremely hydrophobic nature of such lipids may also be useful in the design of floating dosage forms to enhance further therapeutic efficacy of certain drugs. As a result of increased bioavailability of poorly soluble drugs, their doses in such delivery systems can be reduced significantly, which in turn would limit/reduce the extent of side effects/toxicity of the drugs [2]. Particulates such as liposomes can passively accumulate at the site of disease and even in extravascular areas, causing an alteration in the pharmacokinetics of the free drug with further enhancement of the therapeutic index of the encapsulated drugs [20]. Their hydrophobic property may be utilized further for masking the bitter taste of certain drugs by coating [21]. **Table 1** provides a list of drugs with extremely low bioavailability wherein the design of lipid-based formulations may be instrumental in their effective utilization and at the same time would improve the outcome of the therapy [22].

4. Manufacturing advantages of lipids as drug carriers

Apart from the therapeutic advantages, the benefits that lipids offer during formulation development and manufacturing are appreciable. Drugs with very low melting point are difficult to process using conventional solid-dose approaches, especially when the drug is either liquid at ambient temperature, or where the crystalline form of the drug changes under the elevated temperatures or pressures associated with processing (e.g., drying of granules and tablet compression). Under these circumstances, formulations comprising a drug solution in pharmaceutical-grade lipids may be designed that can be directly filled into soft or hard gelatin capsules depending on the physical state of the product. The drug–lipid mixture may even be adsorbed onto solid multiparticulate carriers to impart stability to such critical drugs [23].

The formulation of highly potent drugs into conventional solid dosage forms presents a considerable challenge to the formulator as it is difficult to achieve appropriate content uniformity using simple mixing techniques such as dry blending or wet granulation. By the process of melt-granulation, lipid-based excipients can be helpful in solubilization/dispersion of the drug in the form of a solid solution or dispersion. This results in the generation of an isotropic mixture whose content uniformity in the subsequent products may be controlled accurately by suitable capsule filling technology. An extra advantage of capsule filling of lipid-based particles is the reduction in dust, which may be of particular advantage with both potent and irritant materials.

Table 1. List of drugs with extremely low bioavailability (Rxlist).

Sl. No.	Generic name of drug/s	Brand name	Dosage form	Bioavailability
1	Acamprosate calcium	Campral	Tablets	11%
2	Acebutolol hydrochloride	Sectral	Capsules	40%
3	Acyclovir	Zovirax	Tablets, capsules and suspension	10 – 20%
4	Alfuzosin hydrochloride	Uroxatral	Tablets	49%
5	Aliskiren	Tekturna	Tablets	2.5%
6	Alvimopan	Entereg	Capsules	1 – 19%
7	Amiodarone hydrochloride	Cordarone	Tablets	35 – 65%
8	Atenolol	Tenormin	Tablets	50%
9	Atomoxetinehcl	Strattera	Capsules	63% in extensive and 94% in poor metabolizers
10	Atorvastatin calcium	Lipitor	Tablets	14%
11	Atovaquone	Mepron	Tablets	23 ± 11%
12	Azithromycin	Zithromax	Tablets	38%
13	Bromocriptine mesylate	Cycloset	Tablets	7%
14	Bupropion hydrochloride	Zyban	ER tablets	5 – 20%
15	Buspirone	Buspar	Tablets	Very low and variable
16	Candesartan cilexetil	Atacand	Tablets	15%
17	Carvidilol	Coreg	Tablets	25 – 30%
18	Cefditoren pivoxil	Spectracef	Tablets	14%
19	Clarithromycin	Biaxin	Tablets	50%
20	Clofazimine	Lamprene	Capsules	45 – 62%
21	Darifenacin	Enablex	Tablets	15 – 19%
22	Desmopressin acetate	DDAVP	Tablets	5.0% versus intranasal 0.16% versus intravenous
23	Diclofenac potassium	Cataflam	Tablets	50%
24	Diltiazem hydrochloride	Dilacor-XR	Capsules	40%
25	Dronabinol	Marinol	Capsules	10 – 20%
26	Dronedarone	Multaq	Tablets	4%
27	Eletriptan hydrobromide	Relpax	Tablets	50%
28	Entacapone	Comtan	Tablets	35%
29	Eprosartan mesylate	Teveten	Tablets	13%
30	Famotidine	Pepcid	Tablets	40 – 45%
31	Felodipine	Plendil	Tablets	20%
32	Fluvastatin sodium	Lescol	Capsules, ER tablets	24% (9 – 50%)
33	Hydromorphone hydrochloride	Dilaudid	Oral liquid, tablets	24%
34	Isosorbide dinitrate	Isordil	Tablets	10 – 90%
35	Isradipine	Dynacirc	Capsules	15 – 24%
36	Labetalol hydrochloride	Trandate	Tablets	25%
37	Losartan	Cozaar	Tablets	33%
38	Maraviroc	Selzentry	Tablets	23 – 33%
39	Melphalan	Alkeran	Tablets	25 – 89%
40	Metoprolol tartrate	Lopressor	Tablets	50%
41	Moexipril hydrochloride	Univasc	Tablets	13%
42	Morphine sulfate	Kadian	Tablets	20 – 40%
43	Naltrexone hydrochloride	Revia	Tablets	5 – 40%
44	Nefazodone hydrochloride	Serzone	Tablets	20%
45	Neomycin sulfate	Neomycin sulfate	Tablets	3%
46	Niacin	Niaspan	ER tablets	Dose-dependent and highly variable
47	Nicardipine	Cardene sustained release	SR capsules	35%
48	Nimodipine	Nimotop	Capsules	13%
49	Nisoldipine	Sular	ER tablets	5%
50	Olmesartan medoxomil	Benicar	Tablets	26%
51	Omeprazole	Prilosec	Delayed release capsules	30 – 40%
52	Oxybutynin chloride	Ditropan	Tablets	1.6 – 10.9%
53	Paliperidone	Invega	ER tablets	28%
54	Pimozide	Orap	Tablets	50%
55	Pravastatin sodium	Pravachol	Tablets	17%
56	Propafenone hydrochloride	Rythmol	Tablets	3.4 – 10.6%
57	Propranolol hydrochloride	InnoPran XL	ER tablets	25%

Table 1. List of drugs with extremely low bioavailability (Rxlist) (continued).

Sl. No.	Generic name of drug/s	Brand name	Dosage form	Bioavailability
58	Raloxifene hydrochloride	Evista	Tablets	2%
59	Ramelteon	Rozerem	Tablets	1.8%
60	Ramipril	Altace	Tablets	28%
61	Rasagiline mesylate	Azilect	Tablets	36%
62	Rivastigmine tartrate	Exelon	Capsules, oral solution	40%
63	Rizatriptan benzoate	Maxalt	Tablets	45%
64	Rosuvastatin	Crestor	Tablets	20%
65	Saquinavir mesylate	Invirase	Capsules	4%
66	Sildenafil	Revatio	Tablets	41%
67	Silodosin	Rapaflo	Capsules	32%
68	Sirolimus	Rapamune	Tablets	27%
69	Sulfasalazine	Azulfidine EN-Tabs	Delayed release tablets	15%
70	Sumatriptan succinate	Imitrex	Tablets	15%
71	Tacrine hydrochloride	Cognex	Capsules	17%
72	Tacrolimus	Prograf	Capsules	17 – 23%
73	Tapentadol	Nucynta	Tablets	32%
74	Tegaserod maleate	Zelnorm	Tablets	10%
75	Tenofovir disoproxil fumarate	Viread	Tablets	25%
76	Terbinafine hydrochloride	Lamisil	Tablets	40%
77	Thioguanine	Tabloid	Tablets	14 – 46%
78	Tiludronate disodium	Skelid	Tablets	6%
79	Tizanidine hydrochloride	Zanaflex	Tablets and capsules	40%
80	Trospium chloride	Sanctura XR	Extended release capsules	4.0 – 16.1%
81	Valsartan	Diovan	Tablets	10 – 35%
82	Vardenafil hydrochloride	Levitra	Tablets	15%
83	Verapamil	Calan	Tablets	20 – 35%
84	Verapamil	Covera - HS	Tablets	R-33 – 65% S-13 – 34%
85	Zaleplon	Sonata	Capsules	30%

Transition of the physical state of the ingredients from solid to liquid form is desired during pharmaceutical processing to achieve uniform mixing and homogenous distribution of the active ingredients in the final formulation. Use of organic solvents for this purpose is common in practice. However, excipients and processing techniques, which offer freedom from organic solvents, are preferred owing to the lethal effects, stringent global environmental concerns and regulatory issues involved in the use of such solvents. The physicochemical properties of lipids, waxes and even polyethylene glycols have generated a lot of interest in the pharmaceutical industry as a favorable carrier for drug delivery as they help to avoid the use of organic solvents.

5. Technological advances and industrial applications of various lipid-based oral multiparticulate systems

5.1 Liposomes

Liposomes are closed spherical vesicles consisting of a lipid bilayer that has the flexibility of encapsulating drugs of varying lipophilicity in the phospholipid bilayer, in the entrapped aqueous volume, or at their interface. The liposome diameter varies from 25 nm to 2.5 μm and is regulated by the method of preparation and composition [24]. Depending on their size and number of bilayers, liposomes can be classified into three categories: multilamellar vesicles, large unilamellar vesicles and small unilamellar vesicles. Liposomes can also be classified into five types based on composition and mechanism of intracellular delivery: conventional liposomes, pH-sensitive liposomes, cationic liposomes, immunoliposomes and long-circulating liposomes. Liposomes are used for delivery of drugs, vaccines and genes for a variety of disorders that find applications in infectious diseases, such as leishmaniasis [25-28], fungal infection [29], cancer [30-32] and for brain and lung targeting [33,34]. Anticancer drugs, if administered as such, are toxic and have serious side effects, but their encapsulation into liposomal vesicles significantly diminishes their unwanted properties.

As liposomes are derived from lipids, their oral delivery is highly susceptible to degradation by low gastric pH and breakdown by enzymes and bile salts in the intestine. They may, therefore, be mechanically and sterically stabilized to withstand such a gastric environment, but at the same time must also be capable of delivering the encapsulated drug by means of the normal absorption process. In this context, polymerized liposomes that have the ability to survive

intestinal conditions and can be taken up rapidly by M cells and, subsequently, by macrophages, have been explored as oral drug and vaccine vehicles [35,36]. It has been seen that covalent attachment of specific ligands for M-cell-targeting molecules significantly improves the uptake of liposomes by the intestine [36]. Such approaches may provide a technological basis for the commercial development of oral vaccines and other varieties of macromolecular drug in the near future. Alternatively, the mere presence of lipids may even increase the intestinal absorption process, as it is well established that various micelles, mixed micelles and vesicles that generate as a result of intestinal emulsification increase the solubilization and transport of hydrophobic molecules across the enteric barrier. Also, it is possible that lipids may prevent its enzymatic degradation by inactivation of some enzymes [37]. Although parenteral preparations of liposomes have reached the market, the potential of liposomes for oral delivery is yet to be explored [38]. This section is a discussion of certain important studies wherein different modifications in liposomes have helped to withstand the gastric environment and at the same time have resulted in improved therapeutic efficacy of the administered drug.

5.1.1 *Recent studies related to liposome development for oral delivery*

To enhance the stability of liposomal formulation in gastrointestinal fluids, surface modification of liposomes using different polymers has been reported. Multivesicular liposomes (MVLs), uncoated and coated with *N*-trimethyl chitosan (TMC), containing oxymatrine (OM), a natural quinolizidine alkaloid used clinically for treating hepatitis B, have been studied for their potential use for drug delivery by the oral route. *In vivo* results indicate that the AUC obtained from the pharmacokinetic study of TMC-coated MVLs was ~ 3.26- and 1.96-fold higher than that of OM solution and uncoated MVLs, respectively [39].

In another investigation, alginate-loaded liposomes prepared by a simple dry film hydration technique containing phospholipid dipalmitoyl phosphatidylcholine were fabricated for encapsulating alkaline phosphatase, a model bioactive protein [40]. After 2 h of exposure to simulated gastric pH, it was observed that the activity of enzyme alkaline phosphatase was maintained at a significantly higher level when encapsulated in the alginate-loaded liposomes as compared with that loaded in conventional liposomes, that is, 80% as compared with 55% ($p < 0.05$), respectively. Further, carbopol lectin conjugate-coated liposomes were found to show more bioadhesion than liposomes coated with unmodified carbopol, which increased the pharmacological effect of orally administered calcitonin [41].

A conjugate of folic acid-poly(ethylene oxide)-cholesterol was adsorbed on the surface of liposome prepared by a dehydration rehydration method. This surface modification resulted in a dramatic increase in the oral bioavailability of a moderate size glycopeptide antibiotic – vancomycin – in rat as compared with uncoated liposomes or oral solution. This increase in bioavailability was attributed to the binding of adsorbed folic acid to receptors in the gastrointestinal tract, which resulted in subsequent receptor-mediated endocytosis of entrapped vancomycin by enterocytes [42].

In a study, Al-Meshal *et al.* [43] prepared liposomes of cyclosporine (CSA) composed of dipalmitoyl phosphatidylcholine and cholesterol by a film hydration method and administered them orally to New Zealand rabbits. A significant improvement in the pharmacokinetic parameters was observed in comparison with the commercially available oily oral formulation of CSA (Sandimmune, Novartis Pharma S.A.S., France) at a dose of 15 mg/kg. Liposomes showed a higher rate of absorption and achieved faster time for peak concentration than that of Sandimmune. The mean residence time (MRT) and mean absorption time (MAT) decreased dramatically following the administration of liposomal formulation. Generally, there was less inter-individual variation in the values of rate of absorption, $t_{1/2}\beta$ and MRT when CSA liposomes were orally administered and compared with the administration of Sandimmune. Thus, the above study indicates that an oral liposomal formulation for CSA can be developed to offer the advantages of low variation in bioavailability and faster onset of action.

In another work [44], liposomal oral formulation of insulin was prepared by a film hydration technique and studied for its penetration property in Caco-2 cell monolayer. The results obtained were compared with *in vivo* tests. The effect of sodium taurocholate (NaTC) as a penetration enhancer was also investigated. The results showed that the permeability of insulin was increased across Caco-2 cell monolayer when the liposome NaTC formulation was used. The oral administration of insulin and NaTC-incorporated liposomes, significantly, decreased blood glucose levels. Furthermore, a high degree of *in vitro*/*in vivo* correlation was observed using the Caco-2 cell monolayer model.

The milestones in liposome technology were the development and introduction of the liposome-based parenteral preparations Daunoxome® (Gilead Sciences, Inc., CA, USA), Doxil® (Ben Venue Lab., Inc., OH, USA) and AmBisome® (Gilead Sciences, Inc., CA, USA) in the market during 1995 – 97. The most widely used techniques for the large-scale production of liposomes are lyophilization [45,46], microfluidization (homogenization) [47], proliposome technique [48], detergent dialysis [49] and the heating method [50-52]. Despite the therapeutic efficacy of the dosage form and availability of production techniques, not even a single oral liposome formulation has been commercialized so far. Some of the major problems limiting the development and manufacture of liposomes on an industrial scale are their poor drug encapsulation efficiency, size distribution, batch-to-batch reproducibility, physical and chemical stability, presence of organic solvent residues and difficulties in their removal, and so on. In addition, the high cost of production, high cost of raw materials, especially purified lipids, and

post-manufacturing treatment to remove organic solvents together result in a considerable increase in the price of the product. The above issues need to be addressed seriously in order to establish liposomes as a popular oral dosage form.

5.2 Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are prepared by using lipids capable of regaining their solid-state on cooling. As these nanoparticulate formulations are derived from physiologically compatible lipids, they represent a safe and effective alternative in comparison with conventional polymeric nanoparticles [53]. SLNs for oral drug administration are specifically used to improve the therapeutic efficacy of drugs with low aqueous solubility or bioavailability as these carriers increase the drug's *in vivo* solubilization and uptake by the lymphatic system, by which first-pass metabolism is avoided. They are also capable of sustaining the drug release for a prolonged period of time, which helps to increase patient compliance, and are suitable for localized treatment of the lymphatic system. The different fabrication technologies of SLNs include size reduction techniques such as homogenization (hot and cold) and ultrasonication, the solvent emulsification/evaporation technique and the supercritical fluid method.

5.2.1 *Homogenization and ultrasonication*

Homogenization and ultrasonication are widely used techniques to reduce the size of lipid droplets in an emulsion state [54-57]. Here, the drug is dissolved/dispersed in lipid melt, which is poured into an aqueous phase containing surfactants (as emulsion stabilizer) maintained at a temperature above the melting point of the lipid in order to prevent its solidification. This mixture is then subjected to homogenization using a high-pressure homogenizer, or high shear mixing using an ultra-turrax, or ultrasonication using an ultrasonicator, for a sufficient period of time at the same temperature. During this process the oil droplets undergo size reduction to the scale of nano range. It must be noted that the quantity of surfactants added must be adequate to stabilize the oil droplets, which have an enormously increased surface area after size reduction. The product thus achieved is a nanoemulsion, which is then subjected to cooling to help the lipids crystallize into solid lipid nanoparticles. There are chances that, owing to small particle size and the presence of emulsifiers, the crystallization process in the aqueous phase may be retarded even after the emulsion is subjected to a temperature well below the melting point of the lipid. Such a physical state of lipid is known as 'super-cooled melt'. To avoid misinterpretation of such a 'nanoemulsion' as 'nanosuspension', solid-state characterization of samples should be carried out using X-ray diffraction and differential scanning calorimetry [58].

The major problems associated with the above method involve the leaching of drug into the aqueous phase, degradation of some drug owing to temperature, crystal modification or generation of super-cooled melts. To overcome these issues cold homogenization was adopted wherein the solid solution/dispersion consisting of drug dissolved/dispersed in bulk lipid is primarily milled to microparticles using ball or mortar milling [59,60]. These microparticles are then dispersed into a surfactant solution and subjected to high-pressure homogenization at or below room temperature. The particle size achieved by this method is usually higher than that of hot homogenization.

5.2.2 *Solvent emulsification/evaporation*

In this technique, the drug–lipid mixture is dissolved in a water-immiscible organic solvent [61-63]. The solution is then poured into an aqueous phase containing surfactant and emulsified by homogenization at a temperature sufficient to evaporate the solvent. As the organic solvent evaporates, nanoparticle dispersion is formed by the precipitation of the lipid in the aqueous environment. The particle size of the nanodispersion is dependent on the concentration of the lipid in the system. The main problem with this method is the use of organic solvent, which must be removed until its concentration is within the acceptable limits.

5.2.3 *Supercritical fluid method*

Organic solvents are commonly used in the production of solid lipid nanoparticles to generate a homogenous mixture of the drug and lipid. If these solvents are not removed as per the regulatory guidelines, they may be dangerous for administration. Therefore, to prepare organic solvent-free solid composite lipid/drug nanoparticles, the supercritical fluid method was explored. In this technique, the lipid and drug are dissolved in a suitable organic solvent to form a solution. This is emulsified further in an aqueous medium to form an emulsion having a discontinuous phase of micelles comprising organic solvent, drug and the lipid, and a continuous phase. Finally, the emulsion is treated with a supercritical fluid under suitable conditions to maintain the fluid in a supercritical state, whereby the fluid extracts the organic solvent from the micelles, resulting in the precipitation of solid composite lipid/drug nanoparticles [64].

The final form of the product obtained from the above-mentioned method is an aqueous dispersion. The stability of the SLNs is compromised in this physical state as they are prone to particle aggregation and drug leaching into the external dispersion phase. Therefore, it is recommended that the aqueous dispersion should be converted into a dry powder form by the process of lyophilization. Lyophilization of the SLN dispersion is usually carried out along with optimum quantity of cryoprotectants such as sorbitol, mannose, trehalose, glucose and polyvinylpyrrolidone in order to prevent contact between discrete lipid nanoparticles and thus enhance the product's shelf life. Alternatively, the dispersion may even be spray-dried into a powder and compressed into tablets using necessary excipients [57]. The aqueous dispersion can also be further processed as such by using it as a granulating agent for tablets, as wetting agent in the extrusion process, or as a coating solution in the pelletization (Wuster) process.

The basic excipient other than the solid lipid required for the SLN production is an emulsifier at appropriate concentration, which helps to reduce the surface tension between the lipid and aqueous phase and maintain stability of the formulation. Certain polymers such as polyvinyl alcohol have also been found to prevent particle agglomeration by virtue of their viscosity-imparting property, which helps to arrest particle movement in the dispersion medium [65].

Oral delivery of drugs using SLNs as carrier has gained considerable research interest over the last few decades owing to the different therapeutic benefits that it has demonstrated over the conventional drug delivery system [66-68]. Unfortunately, this delivery system is still in its infancy as it has not been able to reach patients because of several manufacturing issues on the industrial scale. From the manufacturing point of view, the lipid content of the SLN dispersion should preferably not exceed 5% w/v of aqueous phase in order to prevent an increase in the particle size [57]. Therefore, the overall amount of surfactant required per dose of the drug (especially of higher dose) to stabilize the dispersion is very high, varying from 1 to 4% w/v of aqueous phase. This matter needs consideration as an excess amount of surfactant can interfere with the normal physiology of the gastrointestinal membrane [69]. This issue also restricts this dosage form to the delivery of high-potency drugs (as nanodispersion), which can be administered only with minimum amount of surfactant per dose. In addition, the extra cost incurred in the formulation development of a nano-delivery system needs to be justified with its enhanced therapeutic benefits as compared with that of the available conventional dosage form. Moreover, the possible toxic health effects of these nanoparticles associated with human exposure have not been studied properly as there are possibilities that these may cause unintentional human exposure with unknown health effects that cannot be predicted at present [70].

5.3 Self-emulsifying pellets

Self-emulsifying drug delivery systems (SEDDS) are known to improve the oral bioavailability of poorly water-soluble drugs owing to their ability to self-emulsify rapidly into fine oil/water emulsions on gentle agitation in the gastrointestinal fluids [71,72]. In such a system, the lipophilic drug is dissolved in small droplets of oil. The large surface area generated by these small oil droplets enhances the uniformity and rate of diffusion of the dissolved drug across the oil–water interface [73,74]. This reduces the extent of irritation owing to minimal contact between the drug and the gut wall [75-77]. Such systems are generally liquid dosage forms that can be filled into soft gelatin capsules. However, owing to the special in-process controls involved, attempts are being made to incorporate the liquid self-emulsifying ingredients (oil/surfactant/water mixture) into a powder to fabricate a solid dosage form in the form of tablets or hard gelatin capsules. Examples of such solid systems are pellets produced by extrusion/spheronization after granulating with adsorbents such as microcrystalline cellulose, which can finally be filled into hard gelatin capsules [78] or included in microporous or crosslinked polymeric carriers [79].

5.3.1 *Spray-drying*

Solid SMEEDS produced by spray-drying liquid SMEDDS consisting of ethyl oleate, Labrasol, Cremophor RH 40 and nimodipine along with dextran as solid carrier revealed no difference in the droplet size of reconstituted microemulsion between the liquid and reconstituted SMEDDS [80]. The same dose of nimodipine in solid and the liquid SMEDDS resulted in similar AUC and C_{max} values, but the maximum absorption was retarded by the solid SMEDDS. AUC and C_{max}, after oral administration of the solid SMEDDS, was 2.6- and 6.6-fold higher, respectively, compared with those of the conventional tablet. These results demonstrate that the solid SMEDDS has retained the ability to improve bioavailability by effectively releasing microemulsion lipid droplets from the formulation *in vivo*. Similarly, in another investigation liquid SMEDDS consisting of dexibuprofen, Labrasol, Capryol 90 and Labrafil M 1944 CS was spray-dried with colloidal silicon dioxide (Aerosil 200) as solid carrier. *In vivo* results of solid SEDDS and dexibuprofen powder in rats at a dose of 10 mg/kg showed that the initial plasma concentration of drug in solid SEDDS was significantly higher than that of dexibuprofen powder ($p < 0.05$). The solid SEDDS gave significantly higher AUC and C_{max} than dexibuprofen powder ($p < 0.05$). In particular, the AUC of solid SEDDS was about twofold higher than that of dexibuprofen powder. From these results it can be concluded that solid self-microemulsifying systems are a useful solid dosage forms for oral poorly water-soluble drugs [81].

5.3.2 *Wet granulation*

Self-emulsifying pellets composed of microcrystalline cellulose, lactose and nimesulide as model drug with a mixture containing mono- and diglycerides, polysorbate 80 and water, prepared by wet granulation of powder mixture in a high shear mixer have been investigated for the effect of process variables on the pellets characteristics and for the feasibility of scaling-up. The data of *in vitro* absorption experiments demonstrate that pellets composed of oil-to-surfactant ratio of 1:4 (w/w) showed significant improvement in absorption of the drug [82].

5.3.3 *Extrusion–spheronization*

Another method of producing self-emulsifying pellets is the standard extrusion/spheronization technique. This method was used to prepare pellets of C18 partial glycerides, Solutol HS15 and microcrystalline cellulose, which resulted in pellets with good physical (size, shape, friability) and self-emulsifying properties [83]. These pellets, in contrast to pellets lacking Solutol, were able to transfer a lipophilic dye and a spin probe into the aqueous media. The formulation was capable of accelerating the release of the drug diazepam and

achieving a concentration above its saturation solubility. The pellets are capable of transferring lipophilic compounds into the aqueous phase and have a high potential to increase the bioavailability of lipophilic drugs. Bi-layered self-emulsifying pellets were produced by co-extrusion–spheronization consisting of two cohesive layers, one inert layer containing microcrystalline cellulose, lactose and water and another one containing a self-emulsifying system for vinpocetine, a poorly water-soluble model drug. The bi-layered pellets prepared were of two types: type I had the self-emulsifying system located internally and the inert matrix in the external layer, whereas type II contained both layers in opposite order. Although both types of pellet demonstrated optimum characteristics with respect to their size, shape, density, hardness, *in vitro* dissolution and disintegration, and *in vivo* tests, type II pellets revealed relatively improved drug solubility and *in vivo* bioavailability. The physicochemical properties and pharmacokinetic data of the pellets demonstrate that co-extrusion/spheronization can be used successfully to fabricate bi-layered cohesive self-emulsifying pellets of good quality and with improved *in vivo* bioavailability [84]. The equipment used for extrusion–spheronization is presented in **Figure 1**.

5.4 Lipid-based granules/beads/pellets

Drug can be incorporated in lipid excipients as solid solution (for lipid-soluble drugs) or solid dispersions (lipid-insoluble drugs) and, depending on the method of production, the matrix may be granules, pellets or beads. Pellets and beads are multiple unit matrix dosage forms with higher degree of uniformity in their dimensions compared with that of the granules. These formulations may be directly filled into capsules. They are capable of sustaining the drug release and have an advantage over the coated dosage forms as they do not require extra processing steps such as coating and drying. Different processing possibilities have been developed in order to produce lipid-based granules/beads/pellets, namely, melt-granulation spray-congealing, Hot-melt-extrusion, freeze-pelletization and pastillation [85-89].

5.4.1 *Melt-granulation*

Melt-granulation involves high shear mixing of a thermo-softening binder (e.g., PEGs, lipids and waxes) in its molten form along with the drug and excipients, which is further processed (by sifting) to produce granules of a desired particle size distribution [90-92]. The product temperature is maintained above the melting point of binder either by heating the jacket of the container or automatically owing to heat of friction generated by the high speed of the impeller blades. This technique is superior to conventional wet granulation as it avoids the drying phase and helps to conserve time and energy [93]. A solid dispersion of diazepam with PEG 3000/Gelucire 50/13 as molten binder was prepared using the melt-granulation technique. The product showed a significantly higher drug dissolution rate than that of pure drug. The dissolution rate of matrix granules containing Gelucire 50/13 was higher than that of PEG 3000, which could be attributed to the surfactant properties of Gelucire 50/13 [94-96]. Apart from enhancing drug dissolution by forming solid dispersion, lipid-based multiparticulates using paraffin, vegetable oils, natural waxes and glycerides as lipophilic binders are also applicable for sustaining the release rate of embedded drugs [97].

In another technique known as tumbling melt-granulation, meltable (PEG, hydrogenated rapeseed oil and fatty acids) and non-meltable (lactose) excipients were lain on an inert core (nonpareil seeds) using a centrifugal fluidizing coating granulator to fabricate spherical beads. This method does not require any solvent. A powdered mixture of meltable and non-meltable materials is fed gradually and successively onto the seed materials, which are blown with hot slit air using a centrifugal fluidizing bed granulator. As a consequence, the mixture adheres to the seed materials to form spontaneously spherical beads. The bed temperature and particle size of excipients and drug are factors that affect the size distribution and shape of formed beads. It has been observed that the bed temperature during the processing should be maintained at least 5°C higher than the melting point of the meltable material; particle size of both the meltable and the non-meltable materials should be lowered to below one-sixth of the diameter of the seed materials and the mixing ratio of the meltable material in the powdered mixture should be set at an optimum value [98].

The melt-granulation technique has great industrial application as the processing parameters can easily be defined to ensure consistent performance and product quality [99-101]. Although such formulations have the potential to enhance dissolution of poorly water-soluble drugs, certain disadvantages related to physical characteristics restrict their application on a large scale. Difficulty in pulverization, poor compressibility and poor flow properties of solid dispersions are such challenges that limit the success of this technique in developing solid dispersions [102]. To improve their physical properties, inert core materials with excellent flow and good compressibility have been used to adsorb the solid dispersion melt [23,103,104].

Gupta *et al.* prepared solid dispersion granules by a combination of melt-granulation and the surface adsorption technique [23]. Hot-melt-granulation was carried out to adsorb the melt of a poorly water-soluble drug and polyglycolized glycerides (lipid) onto the surface of magnesium aluminosilicate (adsorbent). Apart from dissolution enhancement, this formulation imparted significant improvement in flow and compressibility of the dispersion granules. Ito and colleagues used a similar combination of solid dispersion to prepare oral solid formulations composed of surfactant (Tween® 80, hydrogenated castor oil and labrasol) and different types of adsorbent (microporous calcium silicate, magnesium alminometa silicate and porous silicon dioxide) for gentamycin and lansoprazole [103,104]. These formulations were capable of

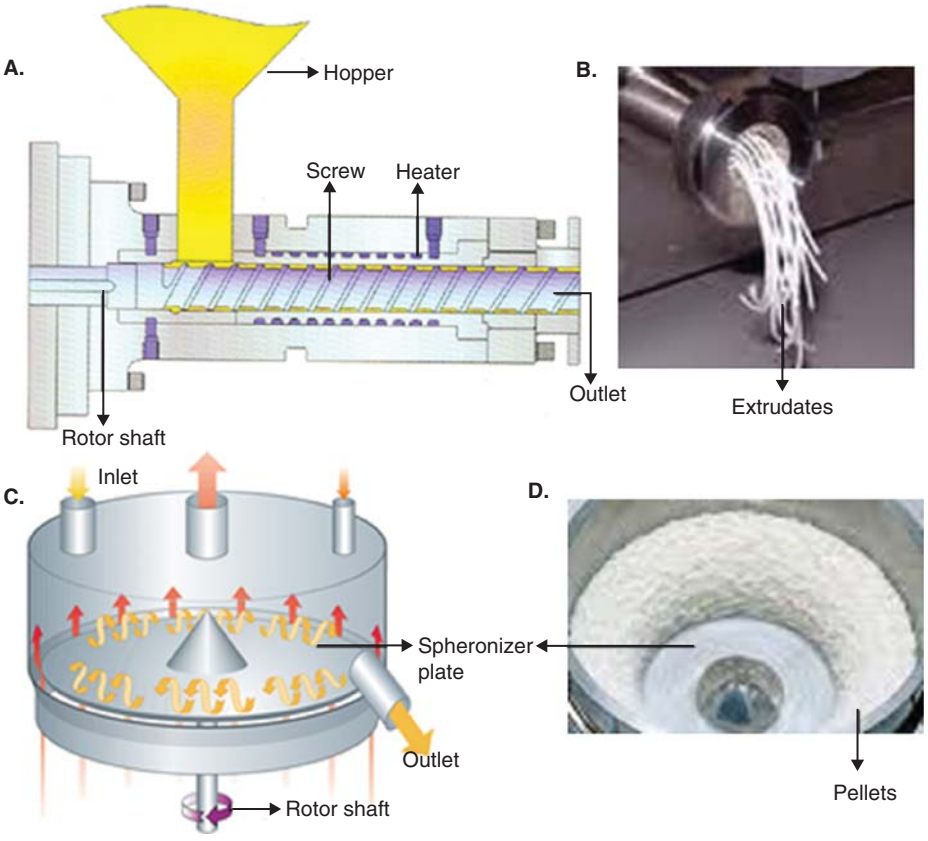

Figure 1. A. Extruder. **B.** Extrudates coming out of extruder. **C.** Spheronizer. **D.** Extrudates being spheronized.

improving the bioavailability of drugs and were found to be dependent on the type of adsorbents and surfactants used. Unfortunately, no information about the physical properties of the blend was reported by the workers.

5.4.2 *Spray-congealing*

Spray-congealing is another process of formulating lipid-based microparticles in which the molten ingredients are sprayed into a cooling chamber. On contact with the cooling air, the molten droplets congeal and recrystallize into spherical solid particles that fall to the bottom of the chamber and are subsequently collected as fine powder. Many types of equipment are available to atomize the liquid mixture and to generate droplets, such as rotary, pressure, two-fluid or ultrasonic atomizers [105]. Recently, most of the research conducted on spray-cooling with lipid-based excipients has been done with ultrasonic atomizers. The important parameters that require attention during the process of spray-cooling include: viscosity of the formulation during atomization, melting point of the excipient, which should range between 50 and 80°C, and the cooling air temperature inside the atomizer, which allows quick and complete crystallization of lipid droplets. The spray-cooling technique can be used for bioavailability enhancement and/or sustained release formulations, depending on the choice of lipid matrix, and the drug behavior in that matrix (solution or dispersion). The drug loading capacity of dispersion is less than that of solution as the formulation viscosity, which plays a significant role in the process of atomization, is comparatively more in the former case. A maximum of 30% drug loading capacity has been reported in the literature [106]. The main class of excipients used in this technique is polyoxylglycerides, and more specifically stearoyl polyoxylglycerides (Gelucire® 50/13). This excipient has been found to facilitate the production of microparticles with narrow size distribution that show significantly enhanced drug release profile for poorly soluble drugs, such as diclofenac or praziquantel [106,107].

5.4.3 *Hot-melt-extrusion and spheronization/ extrusion with solvent*

Hot-melt-extrusion and spheronization uses extruder and spheronizer to produce lipid-based pellets [108-110]. It is a solvent-free process that allows high drug loading as well as content uniformity, especially for low-dose high-potency actives. Traditionally, the method involves the granulation of drug along with other raw materials essentially consisting of at least one excipient with plastic properties (usually microcrystalline cellulose). The wet mass is then passed through an extruder consisting of a die and screen of desired dimensions under constant agitator speed to obtain

spaghetti-like extrudes. These extrudates are spheronized in a spheronizer under constant feed rate and plate revolutions per minute to obtain pellets of uniform size that are finally dried [111,112]. The product is characterized by a reproducible and defined shape and surface [113]. As a modification to this classic formulation, lipids as excipients have been added in order to enhance the dissolution or bioavailability of poorly soluble drugs.

Lipid-based matrix pellets for sustained drug release can also be prepared by extrusion/spheronization using several wetting liquids such as ethanol, castor oil, water or aqueous surfactant solution [114-117]. In comparison, the pellets prepared by melt-extrusion are of very low porosity, which makes them suitable for sustained release matrices with an efficient retardation effect. However, for spheronization the extrudates are required to possess special mechanical properties, such as a certain degree of brittleness, so that the extrudates break into short segments. At the same time, the mass should also possess a certain degree of plasticity to allow the extrudates to spheronize into spherical shaped pellets. Lipids with high melting point can display the above-mentioned mechanical properties at different temperatures. They are brittle at room temperature and soften within a broad temperature range owing to their heterogeneous melting properties, within which they are plastically deformable without sticking. Thus, the spheronization process can be performed in a temperature-controlled double-jacketed spheronizer. The solvent-free extrusion spheronization of mixtures of hard fat and glyceryl trimyristate at different proportions blended with theophylline anhydrous was performed to optimize the effect of various parameters on the sphericity of pellets, as depicted in **Figure 2** [118].

Extrusion spheronization has successfully been tried for 17β-estradiol, methyl paraben and propyl parabens with surfactants such as sucrose monopalmitate (Surfhope® D-1616), lauroyl polyoxylglycerides (Gelucire®™ 44/14) and polysorbate 80 (Tween 80) [119,120]. An innovative 'system-in-cylinder' molding technique was used recently to develop a dual purpose (enhanced bioavailability and controlled release) formulation with propranolol hydrochloride [121-123]. This approach allows lipid-based excipients such as Gelucire 44/14 that possess plastic properties to be used directly in the core of the formulation matrix. The matrix core consisted of a mixture of Gelucire 44/14 and hypromellose molded in an ethylcellulose pipe to protect the core formulation from hydrodynamic and mechanical stresses. The pharmacokinetic studies conducted in dogs confirmed the controlled release of propranolol hydrochloride over 24 h with a fourfold increase in its oral bioavailability versus its commercial formulation.

5.4.4 *Freeze-pelletization*

Freeze-pelletization is another new and simple technique for producing spherical pellets for pharmaceutical application [124-126]. In this technique, the drug is either dissolved or suspended in a carrier/vehicle maintained in its molten state. The melt is then introduced as droplets into a double-jacketed column containing an inert liquid that is immiscible with the melt. Hydrophilic carriers such as macrogols, hydrophobic carriers such as lipids/waxes or a combination of both, which are solid at room temperature and melt below 100°C, can be used. Carriers with lower melting point are preferable to avoid any significant degradation of the actives. Different categories of excipients, such as diluents, disintegrating agents, surfactants, or release-modifying agents, may also be added to modify the drug release behavior of the pellets. The temperature of the liquid in the column is adjusted such that it gradually reduces in the direction of droplets' movement, which allows their gradual solidification into spherical pellets. The density of the droplet with respect to the liquid in the column governs their movement in either an upward or a downward direction. If the density of the carrier/matrix is more than that of the liquid in the column, then the droplets are introduced from the top of the column and the solidified pellets are harvested from the bottom portion of the column, as illustrated in **Figure 3A**. On the other hand, if the density of the carrier/matrix is less than that of the liquid in the column, then the droplets are introduced from the bottom of the column and solidified pellets are collected from the top of the column, as shown in **Figure 3B**.

This technique offers various advantages, such as the pellets formed are non-porous, spherical and uniform in shape, with narrow size distribution. Moreover, it has fewer process variables than other pelletization methods and works as either a batch or a continuous process. The freeze-pelletization technique can be used for the fabrication of both immediate and controlled release matrix pellets by altering the type of drug carrier. Pellets made by this technique may even be coated with suitable polymers to produce pulsatile release, colon-specific formulations, or modified suitably to meet the requirements of a wide range of drug delivery applications for oral administration [126].

Although this technique has the potential for large-scale production of a uniform-sized lipid-based multiparticulate dosage form, it is associated with certain critical issues, the most important being that of drug leaching from the melt into the liquid filled in the column during the process of solidification. As the liquid filled in the column is usually aqueous or mixed aqueous phase to provide an immiscible environment for the hydrophobic (lipid) carriers, part of the drug/s, especially those with water-soluble nature and adsorbed on the surface of the pellets, may be lost during phase transition of the lipid and its transport across the length of the column. Where any solvent other than purified water is used as a cooling liquid, then the process involves the extra step and cost of washing off the solvent. Moreover, the remaining solvents (including the cooling liquid and the washing solvent) in the formulation must be thoroughly quantified to meet the regulatory specifications. Again, the

Process time (s)				
15	300	540	780	1020
Process temperature (°C)				
25.4	34.8	36.6	37.6	38.1
Median aspect ratio				
2.2	2.0	1.6	1.2	1.1
Median equivalent diameter (mm)				
1.85	1.73	1.68	1.56	1.51
10%-Interval				
46.8	58.6	70.2	87.6	87.4
Mean mass per pellet (mg)				
2.50	2.24	2.18	2.15	1.95
Pictures of spot samples				

Figure 2. Properties of pellets after defined process steps (batches contain 27% glyceryl trimyristate at 31°C).
Reproduced with permission from [118].

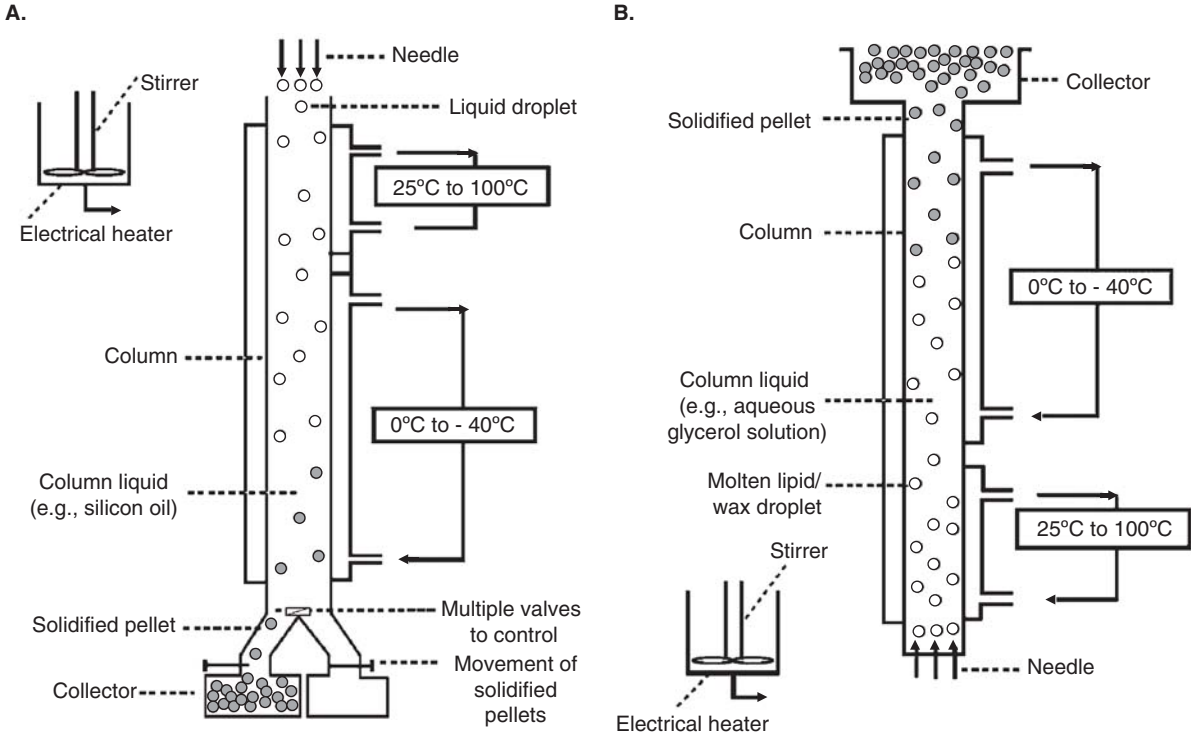

Figure 3. Schematic diagram of freeze-pelletization technique.
Adapted with permission from [124].

leaching of water-soluble drugs during the above-mentioned process of non-aqueous solvent washing from the surface of the pellet cannot be avoided. The designing of a scale-up machinery of this process is yet to receive the attention of manufacturers, and may hopefully find a suitable place in the near future, especially for the production of lipid pellets of water-insoluble drugs.

5.4.5 Pastillation

Pastillation is a widely used technique in chemical, petrochemical and agrochemical industries for the solidification of dusty hazardous powders of chemicals into pastilles (hemispherical solidified units), which eases their handling. In this process, the drops of chemical substances in molten state are deposited on a cooled stainless steel surface for rapid solidification to generate pastilles of uniform dimensions. Depending on the weight of the drops and the physical properties (viscosity and surface tension) of the melt, the drops flatten to a certain extent. The solidified droplet, therefore, has the typical 'pastille'-like shape. The production process for the generation of pastilles is carried out on a large scale with the help of specially designed equipment called a 'Rotoformer' (**Figure 4**) [127].

The first attempt to develop pastilles for drug delivery was carried out in the authors' laboratory, wherein controlled release pastilles were successfully designed [128]. Laboratory-scale equipment was assembled for producing pastilles, as shown in **Figure 5**. The equipment consisted of a glass syringe with stainless steel plunger, metallic hypodermic needle, a metallic plate, heating coil and a transformer. The heating coil was wrapped on the external surface of an open-ended insulated ceramic tube. The syringe with hypodermic needle attached was inserted into the ceramic tube. The assembly was then connected to electricity through the transformer and was arranged over the metallic plate with the help of a burette holder. The metallic plate was cooled using ice cubes. The lipid/PEG melt along with the suspended/molten drug and other required excipients were then poured into the preheated syringe and allowed to fall drop-wise onto the cold plate to generate pastilles. The pressure of the plunger was managed manually to regulate the drop rate. After solidification, the pastilles were scrapped with the help of a sharp metallic scrapper and filled manually into size 'zero' capsules.

The critical parameters involved in this process are roughness of cooling surface, dropping height, rate of cooling and crystallization behavior of the carrier. The physical properties of the lipid that are of interest during the processing are its viscosity, surface tension and density of the melt.

This technique offers many advantages over the previously discussed methods. In addition to the benefits of the other techniques, it is also suitable for hygroscopic drugs as the processing of the ingredients is absolutely free from use of water and it is environment friendly as it does not involve any use of organic solvents. Pastilles are stable and highly uniform in shape, can be produced in a wide range of sizes with diameters ranging from 1 to 30 mm, and are free flowing and ideal for handling, filling and packaging. Pastilles have higher bulk density and better packing properties than powders. The conversion of a bulk molten liquid directly into individual solidified units provides a dust- and solvent-free working environment. This technology requires a single piece of equipment for the entire process (melting of lipid, mixing of drug and required excipients, followed by solidification). In pastillation, energy cost is reduced owing to the absence of associated processes of grinding, crushing or other breaking processes. Pastilles of small dimensions can easily be filled into capsules, whereas the larger ones can either be strip-packed or filled directly into sachets/bottles.

6. Conclusion

The rapidly growing pharmaceutical industry is continuously looking to the development of new active molecules, which inevitably requires a suitable dosage form capable of delivering those molecules effectively in the body. Although several excipients are available for the development of oral formulation, lipids demonstrate an extra advantage of improving the bioavailability of lipophilic and highly metabolized drugs. Therefore, special attention should be diverted to innovate, improve and address the problems associated with the fabrication technology using lipids. Moreover, new dosage form such as pastilles, solid SMEDDS and new technologies such as freeze-pelletization may be used to improve the therapeutic efficacy of certain drugs where other approaches are restricted owing to intellectual property rights. Moreover, use of lipids as the major excipient would also be helpful in reducing the dosage of the drug, especially those of poorly water-soluble nature. Thus, such efforts of formulation scientists would contribute significantly to upgrading the current healthcare system and help patients to make their life easier and healthy.

7. Expert opinion

The objective in designing new dosage forms and upgrading existing fabrication technology is to reduce costs and improve product quality, which would in turn improve patient compliance and reduce the cost of treatment. The area of research in the above-mentioned field is primarily due to the limited number of solid dosage forms available, such as tablets or capsules, for any particular drug. This issue intensifies further with the intellectual property rights for these formulations, which increases their cost and restricts formulation scientists to developing dosage forms for drugs. Finally, it is the patients who sometimes do not receive the treatment or have to spend high amounts to purchase the medication. Therefore, there is a need to design new simple dosage forms and also to upgrade existing manufacturing technology, which can open alternatives and new avenues in the field of drug delivery for

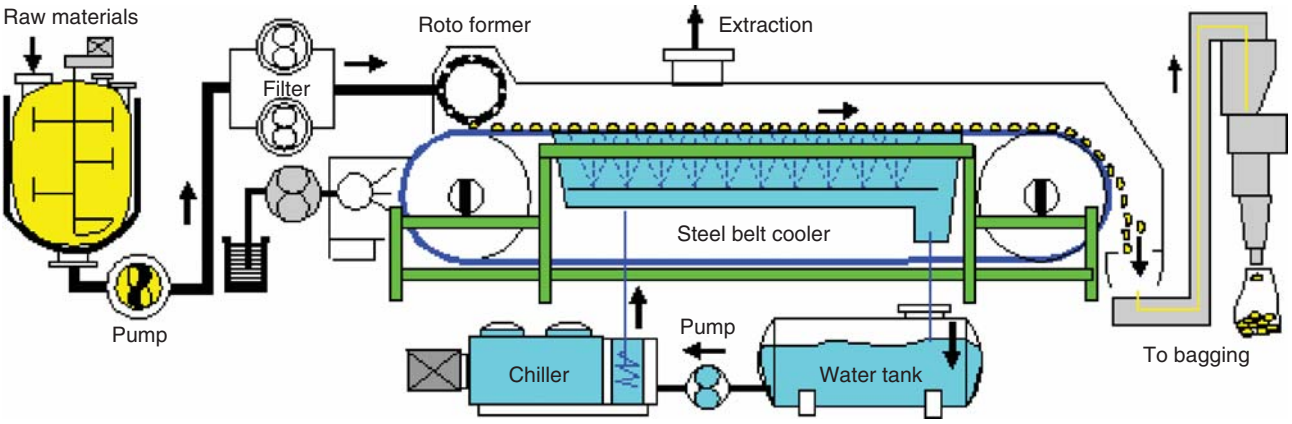

Figure 4. Schematic diagram of pastillation technique.
Reproduced from [127].

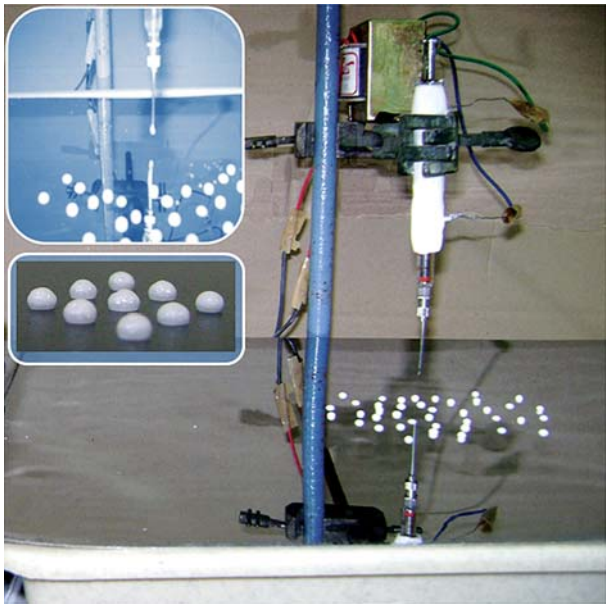

Figure 5. Schematic diagram of laboratory-scale equipment of pastillation developed in-house.

preparing patent non-infringing formulations of existing drug products and help patients to receive the treatment at an affordable price.

Unfortunately, the potential of pastillation technology for the development of oral multiparticulate dosage forms has not been recognized by the pharmaceutical industry. In the absence of application of this unique technology in the pharmaceutical field so far, pastillation can be explored to develop a new dosage form with modified drug release characteristics. The greatest advantages in the development of this dosage form would be the simplicity in its design, solvent-free processing and varied functionality. The availability of existing production facilities in the chemical industry for its commercialization would be an added advantage. Moreover, use of lipids as the major excipient would also be helpful in improving bioavailability and in reducing the dosage of the drug, especially poorly water-soluble drugs. Furthermore, the immediate release pastilles, if amalgamated with appropriate taste and color, would add a new item to the product basket of dosage forms for oral delivery. This dosage form can be used as an alternative to those patented medications that are available on the market at high prices. If implemented, it can also be an alternative for line extension of existing product baskets and also for designing formulations that do not infringe patents.

Declaration of interest

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