INTRODUCTION

The biopharmaceutics classification system (BCS) is a useful mechanism used by researchers for obtaining bioequivalences during in vivo bioequivalence studies and for decision making when determining the required solubility and permeability during drug discovery. This is because BCS is established upon a scientific blueprint highlighting the three rate-limiting steps critical in oral absorption: the liberation of the drug from its dosage form [1], prolongation of the dissolved state along with the whole gastrointestinal (GI) tract [2], and penetration of the drug molecules via the GI membrane into the blood [3]. Additionally, enterohepatic metabolism constitutes a fourth step that affects the systemic accessibility along with the release of metabolites into systemic blood circulation. The biopharmaceutical drug disposition classification system (BDDCS) proposed by Wu and Benet comprehensively describes the absorption operation by including the fourth rate-limiting step of first-pass metabolism. Niosomes are uncharged surfactant vesicles comprising microscopic lamellar structures built upon an amalgamation of uncharged surfactants such as the alkyl or dialkyl polyglycerol ether class and cholesterol formed via subsequent hydration in an aqueous buffer [2]. In niosomes, the vesicle-building amphiphiles are uncharged surfactants e.g., Span 60 that are typically balanced by incorporating cholesterol and miniscule amounts of a negatively charged surfactant such as dicetyl phosphate [4]. Several methods exist for niosome fabrication such as ether injection [5, 6], the hand-shaking method [6], sonication [6], microfluidization [7], reverse phase evaporation [8], the bubble method [9], multiple membrane extrusion [7], and the proniosomal approach [10]. Characterization parameters include particle size, in vitro drug release, entrapment efficiency, and drug content together with some specific characteristics that depend on the formulation mechanism such as skin permeation etc. Herein, a literature survey was performed using accessible databases such as Google Scholar, PubMed, and Scopus to review research articles and thus compile a comprehensive yet concise introduction to the BCS and niosomes along with their applications.

Biopharmaceutics classification system

BCS is a scientific framework for classifying a drug based on its aqueous solubility and intestinal penetrability [11]. When used in conjunction with the in vitro dissolution properties of the concerned drug, BCS considers three important parameters: solubility, intestinal permeability, and dissolution rate. Together these parameters determine the essential factors of the speed and limit of oral drug absorption from immediate-release (IR) solid oral dosage forms [12, 13]. Based on the BCS framework, the drugs can be classified into four basic groups using the criteria of their solubility and permeability toward gastrointestinal tract (GIT) mucosa, as shown in fig. 1. The solubility categorization of a drug in the BCS is determined on the basis of the maximum dosage strength of the IR product. A drug is deemed highly soluble when its maximum dosage strength is soluble in a minimum of 250 ml of water-based media spanning a pH range of 1.0–7.5; otherwise, the drug is deemed a poorly soluble candidate. The volume approximation of 250 ml was established in the literature using traditional bioequivalence study methods [12, 13]. The permeability classification is directly based on a drug’s intestinal absorption limit in humans or indirectly based on the calculations of mass transfer speed via the human intestinal membrane. A drug is deemed highly permeable when the intestinal absorption limit is ≥90%. Otherwise, the drug is deemed poorly permeable [12, 13]. An IR drug is categorized as a fast dissolution product when at least 85% of the stated amount of the drug dissolves in less than 30 min when utilizing the United States Pharmacopoeia (USP) Apparatus I set at 100 rotations per minute (rpm) or USP Apparatus II at 50 rpm comprising a minimum volume of 900 ml of each of the following media: 1) acidic media, such as 0.1 N hydrochloric acid or USP simulated gastric fluid with an absence of enzymes; 2) a pH 4.5 buffer, and 3) a pH 6.8 buffer or USP simulated intestinal fluid in the absence of enzymes. Otherwise, the drug is deemed a slow dissolution product.
Solubility and permeability measurement in the discovery/development settings

Drug discovery begins with the recognition of a pharmacophore by scanning a library of recombinant chemical series through a biological method such as attachment to a receptor or enzyme blocking. The prototypical hit compounds are then directed toward high throughput screening (HTS) pharmaceutical profiling. Compounds with the required biological and pharmaceutical resources are subsequently examined in vivo for confirming the mechanism of action followed by lead optimization via chemical synthesis [14].

Solubility determination

HTS solubility examination typically begins with a dimethyl sulfoxide (DMSO) solution. This stock solution is incorporated into a pH 7 phosphate buffer with a volume of one microliter at all times until the compound precipitates out of the solution [15]. The light scattering phenomenon observed from the precipitated material is detected using an ultraviolet (UV) detector or directly via laser nephelometry [16]. Another method implements equilibration, followed by filtration of the DMSO-buffer suspension. Then, the filtrate is analyzed through a direct UV method. These automatic procedures are currently being commercially used for HTS procedures are again characterized by low (BCS classes III and IV) to high permeability (BCS classes I and II) when entering the development stage. Moreover, the Caco-2 cells require 21 d to fully develop into a monolayer of integrity, whereas other cells such as the Madin–Darby canine kidney (MDCK) require only 3–7 d; hence, the latter have been used more frequently to accelerate the analysis [21]. However, MDCK cells exhibit the same problems as the Caco-2 cells in terms of generating false-negative results and thus could represent low permeability. In addition, the MDCK cells present more issues than Caco-2 cells including less expression of various efflux pumps and failure to meet the criteria for screening of chemical series with identified efflux problems. Both the in vitro Caco-2/MDCK cell lines method and the in situ rat perfusion methods are trusted by the FDA in terms of BCS classification.

Niosomes

Niosomes are microscopic layered structures of 10–1000-nm size, and their core is environmentally friendly and non-reactive toward the human immune system and biocompatible surfactants [22]. The niosomes are amphipathic, i.e., a water-soluble drug can be locked in their core cavity region and water-insoluble drugs in the non-polar region are present inside the bilayer; hence, both water-soluble and water-insoluble drugs can be added into niosomes as shown in fig. 2. Structurally, niosomes are similar to liposomes: they possess the same drug delivery potential and offer more chemical stability than liposomes at lower production costs. Both vesicles comprise a bilayer, which is composed of uncharged surfactants in the case of niosomes and of phospholipids in the case of liposomes.

Fig. 2. Structure of niosome. Adapted from Reference [23]. Copyright License obtained under CC BY license (https://creativecommons.org/licenses/by/4.0/)

Preparation methods

Ether injection method

The primitive step in niosome formulation via the ether injection method involves surfactant dissolution in any volatile solvent such as diethyl ether, chloroform, or methanol. The solution is then incorporated into an aqueous drug solution via injection using a 14 Gauze needle maintained at 60 °C on a water bath or on a magnetic stirrer. Consequently, monolayered vesicles with sizes ranging from 50 to 1000 nm are produced through the volatile solvent’s atomization [24].

Hand-shaking method

The hand-shaking method, also known as the thin-film hydration technique, involves the dissolution of the surfactant and cholesterol in a volatile organic solvent and subsequent transfer into a rotary mixer.
evaporator. Following evaporation, a thin layer of solid remains on the wall of the flask. This dried layer is then rehydrated using an aqueous phase of the drug of interest. Alternatively, this procedure can be performed at room temperature via light agitation [6, 25].

**Sonication**

Niosomes can be fabricated by sonicating an amalgamation of surfactant, cholesterol, and an aqueous phase containing the drug maintained at 60 °C for 3 min in a beaker placed in a probe or bath sonicator. The vesicles thus formed have less particle size exhibit size uniformity [6, 25].

**Microfluidization**

Microfluidization is another duplicable method that yields size uniformity via operating, i.e., two fluidized streams flowing forward and intersect with each other at ultrahigh speeds through an accurately defined microchannel [24, 25, 7].

**Reverse-phase evaporation method**

The reverse-phase evaporation method utilizes an amalgamation of surfactant and cholesterol in a 1:1 ratio in addition to ether and chloroform. An aqueous phase containing the target drug is incorporated into the concoction followed by sonication at a temperature of 4 °C–5 °C. Sonication is continued for about 5 min after incorporating about 10 ml of phosphate-buffered saline into the concoction. The organic solvent is atomized at 40 °C under low pressure, and the persisting suspension is thinned using phosphate-buffered saline. The amalgamation is heated at 60 °C for 10 min, and the ultimate product of niosomes is attained [24, 25, 8]. Fig. 3 shows a schematic of this method.

**The bubble method**

Niosomes can also be fabricated in the absence of organic solvents through the bubble method, wherein a bubbling unit containing a round-bottomed flask with three necks is placed in a water bath; a water-cooled reflux condenser and thermometer are placed in the first and second necks, respectively, whereas nitrogen gas is introduced through the third neck. Surfactant and cholesterol amalgamated at 70 °C in a buffer are blended and bubbled at 70 °C by introducing nitrogen gas into the apparatus [24, 9]. Fig. 4 shows a schematic of this method.
Multiple membrane extrusion method
In the multiple membrane extrusion method an amalgamation of surfactant, cholesterol, and dicetyl phosphate is dissolved in chloroform, and the resulting concoction is vaporized to form a thin film. This film is dampened with an aqueous drug solution, and the resulting suspension is extruded using polycarbonate membranes, which are inserted in series to create a maximum of 8 passages [24, 25, 27].

Prioniosomal method
In this niosome fabrication method, a water-soluble transporter such as sorbitol is sprayed with a surfactant to form a dry formulation in which each water-soluble particle is laminated with a thin layer of dry surfactant. This formulation is labeled as a prioniosome. The prioniosome powder thus formed is subsequently loaded into a screw-capped vial, and blended with water or saline at 80 °C by vortexing. This is followed by stirring for about 2 min, thus producing the final niosomal suspension [28].

Niosome evaluation

Entrapment efficiency
For assessing a drug’s entrapment efficiency within the niosomes, any of the following three methods can be used: centrifugation, gel filtration, or complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100. This method estimates the quantity of the drug remaining locked inside the niosomes and examines the final solution throughput an assay method suitable for the target drug. In this method, entrapment efficiency (EF) can be defined as follows [29].

Percentage drug entrapment (%) = \frac{\text{Total Drug Content (mg) - Free Drug Content (mg)}}{\text{Total Drug Content (mg)}} \times 100

Drug content
The fabricated niosomal formulations are transferred into a test tube in which 10 ml of methanol is introduced to break down the niosomes followed by the destruction of the outer membrane, thereby liberating the entrapped drug. The quantity of the released drug can be estimated using a UV spectrophotometer at a specified wavelength, thus enabling the calculation of the total mass of drug present in the formulation [30, 31].

In vitro drug release
The in vitro release rate can be determined using a dialysis tube. In this method, a dialysis sac is cleansed and immersed in distilled water. The niosome suspension is transferred using a pipette inside a bag composed of the dialysis tubing and fastened; then the bag left in a 200 ml buffer solution placed in a 250 ml beaker and subjected to continuous vibration at 25 °C or 37 °C. The drug content in the resulting buffer solution is assessed at various time points via a suitable assay method [32].

Particle size and morphology
The most commonly used methods for determining particle size and the morphology of niosomes are dynamic light scattering (DLS) [33], scanning electron microscopy (SEM) [34], transmission electron microscopy (TEM) [35], freeze-fracture replication-electron microscopy (FF-TEM) [36], and cryotransmission electron microscopy (cryo-TEM) [37]. DLS simultaneously provides detailed information on particle size and critical information on the solution’s homogeneity. A single sharp peak in the DLS result indicates the presence of a single population of scatters. The polydispersity index (PI) is a useful parameter in this regard. If PI≤0.3, then homogeneous population exists in the colloidal system and if PI=0.3 then the system is not homogeneous [33]. The abovementioned microscopic methods are commonly used to evaluate niosome morphology.

Niosome applications

Sustained release
A constant concentration of drugs possessing a narrow therapeutic index and low water solubility can be maintained in the blood plasma via niosomal encapsulation, thus achieving sustained release action. Azmin et al. [38] Proposed using part of the liver as a storage site for the absorption of methotrexate after niosome administration by the liver cells, thereby realizing sustained drug release.

Localized drug action
Niosomal dosage is an attractive method to localize drug action at the administration site because of the size of niosomes and their lesser penetrability compared with liposomes epithelial and connective tissue. This improves the drug’s effectiveness and reduces its systemic toxic effects. For example, antimonials entrapped within niosomes are absorbed by mononuclear cells resulting in localized drug action, potency enhancement, and dual reduction in dosage as well as toxicity [9, 39].

Cancer
Common limitations of cancer chemotherapy manifest as side effects and less therapeutic efficacy. Doxorubicin, a broad-spectrum anthracycline used for anticancer activity, has demonstrated a dose-dependent irreversible cardiotoxic effect [4]. However, when this drug was administered in the form of niosomes to mice possessing an S-180 tumor, the lives of the mice were prolonged and the multiplication of sarcoma was reduced. This can be attributed to the high effectiveness of niosomes in drug entrapment, resulting in sustained blood circulation and changes in drug metabolism [4, 40].

Another popular anticancer drug, daunorubicin hydrochloride, demonstrated increased anticancer activity in its niosomal entrapped form when compared against the effectiveness of the drug alone. The niosomal formulation constructively shunted Dalton’s ascitic lymphoma cells in a short duration. In the case of bleomycin, a potent anticancer drug, compared with its free drug form, the form of the drug entrapped within niosomes comprising 47.5% cholesterol accumulated in high levels at the tumor position [41]. Methotrexate is a well-known toxic synthetic antineoplastic drug used in chemotherapy, either alone or in conjunction with other medications, to cure different types of cancers. Extensive research has demonstrated that intravenous administration of methotrexate entrapped in niosomes to S-180 tumor-bearing mice causes total regression of the tumor, relaxed drug clearance, and an elevated plasma level of methotrexate [42]. Improved drug penetration was observed when 5-fluorouracil was developed in bola-surfactant niosomes to cure skin cancer [43]. In addition to the fact that boosted antitumor activity is observed, in some situations, drug entrapment in niosomal vesicles reduces the cytotoxicity toward normal cells, as reported in a study on the effect of niosomes containing vincristine on the side effects of the drug, such as neurological toxicity, diarrhea, and alopecia, were reduced, whereas antitumor activity was increased in a mouse model of S-180 sarcoma after niosome-entrapped vincristine was administered [44]. Tocotrienol was the foremost drug to be reported for its anticancer activity in the initial years of the 1990s, and was subsequently entrapped in niosomes by Fu et al. [45]. Applying the film hydration method double (at minimum) the cytotoxic effect of niosomal tocotrienol in shattering breast cancer cells with the cells’ drug absorption improving 2.5-fold. The antitumor activity of the preparation was also observed in female BALB/c nude mice carrying breast cancer cells [46]. Curcumin is well known to demonstrate many therapeutic uses, including anticancer properties [47]. A new niosome system comprising Span 80, Tween 80, and poloxamer 188 was demonstrated to have excellent encapsulating efficiency (92.3%) with respect to curcumin. When niosomal curcumin was incorporated into ovarian cancer A2780 cells, it increased cytotoxic and apoptotic activities as compared with freely used curcumin. This can be attributed to the property of controlled liberation of curcumin from niosomes [48]. Sharma et al. [49] Fabricated niosomes using Tween 80 and cholesterol through a film hydration method. Two anticancer drugs, curcumin and doxorubicin hydrochloride, were entrapped within the niosomes; while curcumin was found to be accumulated in the shell, doxorubicin in hydrochloride would be found to be accumulated in the inner aqueous core of the niosomes. Higher cytotoxicity toward cervical cancer cells (HeLa cells) was observed for the double-drug-encapsulated niosomes. Artemisinin, which is extracted from the Chinese herb Artemisia annua, is frequently used in the treatment of fevers and chills [50]. The herb was...
also has antitumor properties [51]. However, the use of artemisinin is limited because of its low solubility in water and oil coupled with various cancers such as leukemia, lymphoma, breast and prostate cancers, and multiple sclerosis. However, the administration of this drug is commonly followed by serious systemic toxicity, mainly cardiotoxicity. Tila et al. [56] prepared pH-sensitive, polymer-modified, and plasma-stable niosomes to deliver this drug. The cytotoxicity of mitoxantrone niosomes was examined against human ovarian cancer (OVAR-3), human breast cancer (MCF-7), as well as human umbilical vein endothelial cell lines. Mitoxantrone entrapped in the pH-sensitive niosomes demonstrated increased cytotoxicity when compared against traditional niosomes on the cancer cells, but showed lesser cytotoxic activity when used on the endothelial cell line. These results demonstrate niosomal formulations to be promising carriers in minimizing the side effects of mitoxantrone. Cisplatin, a commonly used anticancer drug, acts by starting apoptosis and necrosis of the cells. However, the use of cisplatin is accompanied by various harmful side effects, mainly nephrotoxicity and neurotoxicity [57]. Furthermore, the emergence of drug resistance toward cisplatin in patients is a significant issue in the cancer therapy of patients. Niosomal cisplatin manufactured via reverse-phase evaporation exhibited a 1.5-fold boost in cytotoxic activity against BT-20 breast cancer cells when compared against the unencapsulated drug [58]. Antineoplastic effects of the niosomal formulations mentioned above are summarized in table 1.

### Table 1: Antineoplastic effects exhibited by various niosomal formulations

| Drug                                      | Action shown                                                        | References |
|------------------------------------------|                                                                    |            |
| Doxorubicin                               | Reduced proliferation of sarcoma cells                             | [4, 40]    |
| Daunorubicin Hydrochloride                | Shattered Dalton's ascitic lymphoma cells                         | [41]       |
| Bleomycin                                 | Collected in high levels at the tumor site                         | [41]       |
| Methotrexate                              | Improved antitumor activity against sarcoma                       | [42]       |
| 5-Flourouracil                            | Improved drug penetration in skin cancer treatment                 | [43]       |
| Vinorelbine                               | Improved antitumor activity against sarcoma                       | [44]       |
| Tocotrienol                               | Improved cytotoxicity toward breast cancer cells                   | [46]       |
| Curcumin                                  | Improved cytotoxic and apoptotic effects toward ovarian cancer cells| [49]       |
| Curcumin and Doxorubicin Hydrochloride    | Improved cytotoxicity toward cervical cancer cells                 |            |
| Artemisin                                | Cytotoxicity toward melanoma cells                                | [53]       |
| Tamoxifen citrate                         | High cytotoxicity against breast cancer cell line                  | [55]       |
| Mitoxantrone                              | High cytotoxicity against human ovarian cancer and breast cancer cell lines | [56] |
| Cisplatin                                 | Improved cytotoxicity toward breast cancer cells                   | [58]       |

### Ophthalmic drug delivery

Bioadhesive-coated niosomal formulation of acetazolamide fabricated from Span 60, cholesterol stearylamine, or dicetyl phosphate shows more affinity toward decreasing the intraocular pressure when compared against marketed formulation (Dorzolamide); in contrast, the chitosan smeared niosomal formulation timolol maleate (0.25%) demonstrates more activity in decreasing the intraocular pressure than marketed formulation with the reduced possibility of cardiovascular side effects [59].

### Delivery of peptide drugs

Yoshida et al. [60] probed into the oral delivery of 9-desglycinamide, 8-arginine vasopressin as a model drug using niosome and by employing an in vitro intestinal loop model and enhanced the stability of peptide.

### Hemoglobin carriers

Niosomes can be employed as hemoglobin carriers. The formulated niosomal suspension demonstrated a visible spectrum that can be superimposed over free hemoglobin. Vesicles are open for oxygen to travel inside the molecule and the hemoglobin dissociation curve can be altered similar to that of non-entrapped hemoglobin [61, 62].

### Antiviral drug delivery

Furthermore, niosomes can deliver various antiviral drugs. Ruckmani and Sankar [63] prepared zidovudine encapsulated niosomes and assessed their entrapment efficiency and sustainability of drug release. The niosomes comprised Tween 80, Span 60, and cholesterol in various proportions. Niosomes comprising Tween 80 exhibited greater entrapment of zidovudine while the addition of dicetyl phosphate improved drug release for a longer duration. The drug outflow from Tween 80 containing formulations maintained at room temperature was substantial when compared to niosomes stored at 4 °C for 90 d. Regardless, a pharmacokinetic study conducted on rabbits also verified that Tween 80 formulations prepared with dicetyl phosphate can be removed from systemic blood circulation in less than five h [64].

### Transdermal drug delivery

Transdermal drug delivery is the delivery of drugs via the skin. The advantage of this delivery route is that transdermally administered drugs fail to undergo the first-pass metabolism; however, the penetration of drugs occurs slowly through the skin and this limitation can be resolved using niosome preparations. The mechanism obeyed by the niosomes for transdermal drug delivery is as follows.

- **Diffusion via the stratum corneum layer.**
- **Water concentration in the skin is critical to this mechanism.**
- **The lipophilic drugs transverse the stratum corneum through various mechanisms such as aggregation, fusion, and adhesion.**
- **Nonionic surfactants improve the permeation thereby improving drug permeation via the skin** [65, 66].

### Niosomes as drug carriers

Niosomes have also been employed as carriers for ibotritol, a diagnostic agent used in X-ray imaging. Topical niosomes can be altered similar to that of non-entrapped hemoglobin [61, 62].

Sawant et al.  
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membrane barrier for the alteration of systemic drug absorption [67].

Niosomes in vaccine delivery

A] Protein subunit vaccines

The development of novel, safe, and efficacious vaccines, is a crucial aim for scientists worldwide. Subunit proteins or the deoxyribonucleic acid (DNA) of multiple organisms are less harmful than live organism-based vaccines, which may be relatively less clinically efficient. Adjuvants are being used in vaccines to improve the immunogenicity of the subunit vaccines via protection (i.e., preventing the destruction of the antigen in vivo) and upgraded targeting of these antigens to the desired antigen-presenting cells [68]. Brewer and Alexander [69] announced the first implementation of niosome antigen distribution for the immunization of Balb/c mice to develop resistance toward bovine serum albumin (BSA). They concluded that niosomes were possibly superior stimulators of the Th1 lymphocyte subset when bovine serum albumin (BSA). Hassan et al. [70] observed against homologous (type 2 herpes simplex virus HSV-2) CHOL/DCP niosomes in mice. In contrast, only partial protection was desired antigen-presenting cells [68]. Brewer and Alexander [69] of the antigen

Adjuvants are being used in vaccines to improve the immunogenicity based vaccines, which may be relatively less clinically efficient. A

CONCLUSION

B] DNA vaccines

DNA is a nucleic acid (biomolecule) that contains the genetic code specifying the biological development of all cellular forms of life and is often referred to as the molecule of heredity as it is responsible for the genetic propagation of all traits [84]. The fundamental principle of DNA vaccination is to induce immunity by transfecting host cells with plasmid DNA encoding the required antigen, contrary to the typical approach of injecting an antigen in the form of a protein or peptide [85]. Dengue ribonucleic acid has been discovered to possess more than five stereotypes [86]. DNA encapsulation in niosomes can be attributed to the shielding of genetic material in the biological environment, enhancing significant humoral as well as cell-mediated immune responses against the encoded antigen in immunized mice [87]. Perrie et al. [88] announced the encapsulation of nucleoprotein demonstrating the plasmid of the H3N2 influenza virus in NSVs followed by subcutaneous injection of the formulations that improved the immunization of treated mice relative to naked DNA. Vyas et al. prepared Span 85/CHOL niosomes containing DNA encoding HBsAg, which enhanced the serum anti HBsAg titer and the cytokine levels (IL-2 and IFN -

All Authors have contributed equally.

AUTHOR CONTRIBUTIONS

All Authors have contributed equally.

FUNDING

Nil
CONFLICT OF INTERESTS

None

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