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Review

Nanotechnology as a tool to overcome the bariatric surgery malabsorption

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ABSTRACT

Obesity is a metabolic disease that affects all ages; it is considered life-threatening condition as it leads to fatal complications such as; cardiovascular diseases and diabetes. The therapeutic options include; life-style modifications, pharmacotherapy intervention, and surgical intervention. Bariatric surgery (BS) is considered as the most effective option among the others for its rapid weight loss, maintaining the lost mass, and improving the quality of life of the patients. Nevertheless, BS leads to severe changes in the bioavailability of medications, especially for chronic diseases, which may reach to limit where the patient's life endangers. Recently, pharmaceutical formulations had developed several methods to improve the drug bioavailability of drugs though the implying of nanotechnology. Nonotechnology is responsible for reducing the size of the drugs to the nano range (<1000 nm), which increase the drug surface area, dissolution, absorption, and, most importantly, the bioavailability of these drugs. It is believed that BS malabsorption and drugs bioavailability problems can be solved using nanotechnology for its advantages in overcoming BS complications.

Contents

Abbreviations: BS, Bariatric Surgery; MBI, Body Mass Index; WHO, World health organization; T2DM, Type 2 Diabetes Mellitus; RYGB, Roux-en-Y gastric bypass; VA, veteran affairs; ASMBS, American Society for Metabolic and Bariatric Surgery; JIB, Jejunoileal bypass; LAG, Laparoscopic Sleeve Gastrectomy; AGB, Adjustable Gastric band; MIC, Minimum Inhibitory Concentration; DDS, Drug Delivery System; GIT, Gastrointestinal Tract; CFR, Code of Federal Regulations; SCF, supercritical fluid; SNEDDS, selfnanoemulsifying drug delivery system; ISCRPE, improved supercritical reverse phase evaporation; GRS, Generally Recognized as Safe; FDA, Food and Drug Administration.

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1. Obesity

Obesity is one of the metabolic syndromes that had been growing aggressively in the past three decades. Obesity is defined by The Body Mass Index (BMI), which is calculated by dividing the body weight in kilograms (Kg) by the square of the height in meters (m) (Obese $\geq$ 30) (Alqarni, 2016). Globally, Obesity is considered an emerging issue, as reported by the World Health Organization (WHO). In 2008, it was stated that over 1.5 billion adults were overweight, and 500 million of them were obese (Mahmood and Arulkumaran, 2013. Also, childhood obesity is rising rapidly; it is an epidemic in some nations. Approximately 22 million children under the age of 5 years, worldwide, are expected to be overweight in the near future (Alqarni, 2016). In Saudi Arabia, in every 10 adults, 8 are considered overweight or obese, and the issue is dramatically evolving (Alqarni, 2016). Worth mentioning, Al-Quwaidhi et al. study regarding the rate of obesity growing in the kingdom, and his findings indicates that by 2022, the obesity will increase by 41% in men, and 78% in woman, which means a significant health complications, and thus, economic crises due to the special care such patient's needs (Al Quwaidhi et al., 2014).

Globally and according to the statistical data produced in 2016 from Central of Disease Control and Prevention (CDC) associated with National Institute of Diabetes and Digestive and Kidney Disease (NIH) in United State, the prevalence of obesity in adults reach 39% and in children aged from 2 to 19 years it reached 18% (Centers for Disease Control and Prevention. Overweight and 0besity. https://www.cdc.gov/obesity/index.html. Accessed Feb-15, 2020).

Obesity is associated with many health problems and serious diseases. Type 2 Diabetes Mellitus (T2DM) incidents in obese adults are considered 35% higher than normal-weight individuals (Nguyen et al., 2011). Obesity also provokes cardiovascular diseases, such as; Hypertension (do Carmo et al., 2016), Dyslipidemia (Grundy and Barnett, 1990), Coronary Heart Disease (Nordestgaard et al., 2012), Heart Failure, and strokes Kenchaiah et al., 2002. Concomitantly, vitamin D deficiency in obese adults is at higher rates than healthy adults, which leads to chronic diseases such as Hyperthyroidism (Vanlint, 2013).

Obese patients show more vitamins (water-soluble and fat-soluble) deficiencies that other patients, this phenomenon is a result of the high numbers of adipose tissues that obese patients have. These individuals are more susceptible to increase secretion of inflammatory adipokines that adipose tissue responsible as they considered as endocrine and metabolic organs. According to Thomas-Valdés et al. (2017), most vitamins are deficient in obese individuals, especially the fat-soluble vitamins, folic acid, vitamin B12 and vitamin C. this deficiency had a severe complication of patients' health, which may contribute in homocysteine metabolism due to their atherogenic potential (Thomas-Valdés et al., 2017).

Treatment choices for obesity include non-surgical treatment and bariatric surgery. Regarding the non-surgical procedure, the approach requires a lifestyle modification (diet, increase physical activity, decrease energy intake, and behavioral changes) along with various pharmacotherapy (Peckmezian and Hay, 2017). This option takes time to show results and is inconvenient for a patient with chronic diseases that may interfere with their ability to do exercises. While on the other hand, Bariatric Surgery merged recently as a fast, reliable, and more convenient option for rapid weight loss and maintaining these conditions (Buchwald and Williams, 2004).

2. Bariatric surgery

In 1998, Dr. Scopinaro published the first-ever known bariatric surgery, and it was followed by reports done by Buchwald and Oien in 2004 (Buchwald and Williams, 2004) and 2009 (Buchwald and Oien, 2009). Bariatric surgery (BS) is the most effective therapy against obesity, and recently it was recommended for type 2 diabetes as a therapeutic plan. BS includes; Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and laparoscopic adjustable gastric banding has gained the attention of most healthcare providers in elevation the issue of obesity for its ease and fast results, especially with patients with mobility problems and those with high risk to develop chronic diseases (Buchwald and Williams, 2004; Buchwald and Oien, 2009).

The multitude of research had confirmed the efficiency of bariatric surgery in reducing body weight and maintaining the loss and thus improving the quality of life due to the improved health of these individuals. Moreover, a study had shown the ability of bariatric surgery to reduce the risk of death morbidly obese individuals by 89%. In that study, bariatric patients showed less frequency of admissions to the hospitals and better general health when compared to the other non-bariatric surgery patients (Sherman, 2013; Christou et al., 2004).

A Canadian research group studied the urgent need for bariatric surgery by addressing the main reason for shifting the pharmacological therapy option into surgical intervention. That study had evaluated the results of lifestyle modification, pharmacological treatment, supplements treatment, and bariatric surgery. The researchers concluded and recommended applying bariatric surgery over the other treatment choices for its high percentage of success and patient compliance (Karmali et al., 2010).

Another clinical trials has been done by Donald and other co-workers (Simonson et al., 2018). They studied the effect of RYGB surgery on diabetic patients Type II compared to those follow an intensive lifestyle management program. The results showed a significant reduction in both weight and blood sugar. In addition, patients with RYGB surgery required less medication for diabetes, blood pressure and cholesterol, and thus, the risk of heart disease reduced significantly in RYGB patients compared to intensive lifestyle program patients (Simonson et al., 2018).

A group of researchers at the University of Washington had studied the association between BS and long-term survival of the patients. The study was retrospective cohort which used data from veteran affairs (VA) that undergone BS (n = 2500) and compared it to control patients (n = 7462) using sequential stratification and an algorithm that included age, sex, geographic region, body mass index, diabetes, and Diagnostic Cost Group. The mean age was 52, 53, respectively, while BDI was 47, 46, respectively. The follow-up analysis was in three main time points; short ($\leq$1 year), midterm (>1–5 years), and long-term (>5 years). For BS patients, Kaplan-Meier estimated mortality rates were 2.4% at 1 year, 6.4%

at 5 years, and 13.8% at 10 years. While it was, 1.7% at 1 year, 10.4% at 5 years, and 23.9% at 10 years for controlled patients. These results provide reliable evidence of BS's ability to reduce the risk of death and to enhance the quality of life (Arterburn et al., 2015).

A research group at the Bariatric and Metabolic Institute, Cleveland Clinic, investigated BS versus Intensive Medical Therapy for type 2 diabetes (1 and 5 Year Outcomes), for both studies, the researchers used randomization of 150 obese patients with uncontrolled type 2 diabetes using intensive medical therapy alone and with BS. The BDI for the patients was between 27 and 43, and the mean age was 49 years. The primary outcome was glycated hemoglobin level of 6% for both patients. The result of these 2 studies showed a significant decrease with BS rather than intensive therapy alone, which indicates the necessity of BS in controlling type 2 diabetes (Schauer et al., 2014; Singh et al., 2009).

According to the American Society for Metabolic and Bariatric Surgery, the most common BS are; gastric bypass, sleeve gastrectomy, adjustable gastric band, and biliopancreatic diversion with duodenal switch. (American Society for Metabolic and Bariatric Surgery. Bariatric Surgery Procedures. https://asmbs.org/patients/bariatric-surgery-procedures (accessed Feb 15, 2020).

2.1. Gastric bypass

It is the most common BS, and it is considered a gold standard for weight loss which also known as Roux-en-Y gastric bypass (RYGB). The procedure of this BS is by creating a small pouch of the stomach (300 mL capacity) connected directly to the jejunum by bypassing duodenum, as shown in Fig. 1. RYGB has many advantages such as; alteration of guts hormones, which reduces the appetite and

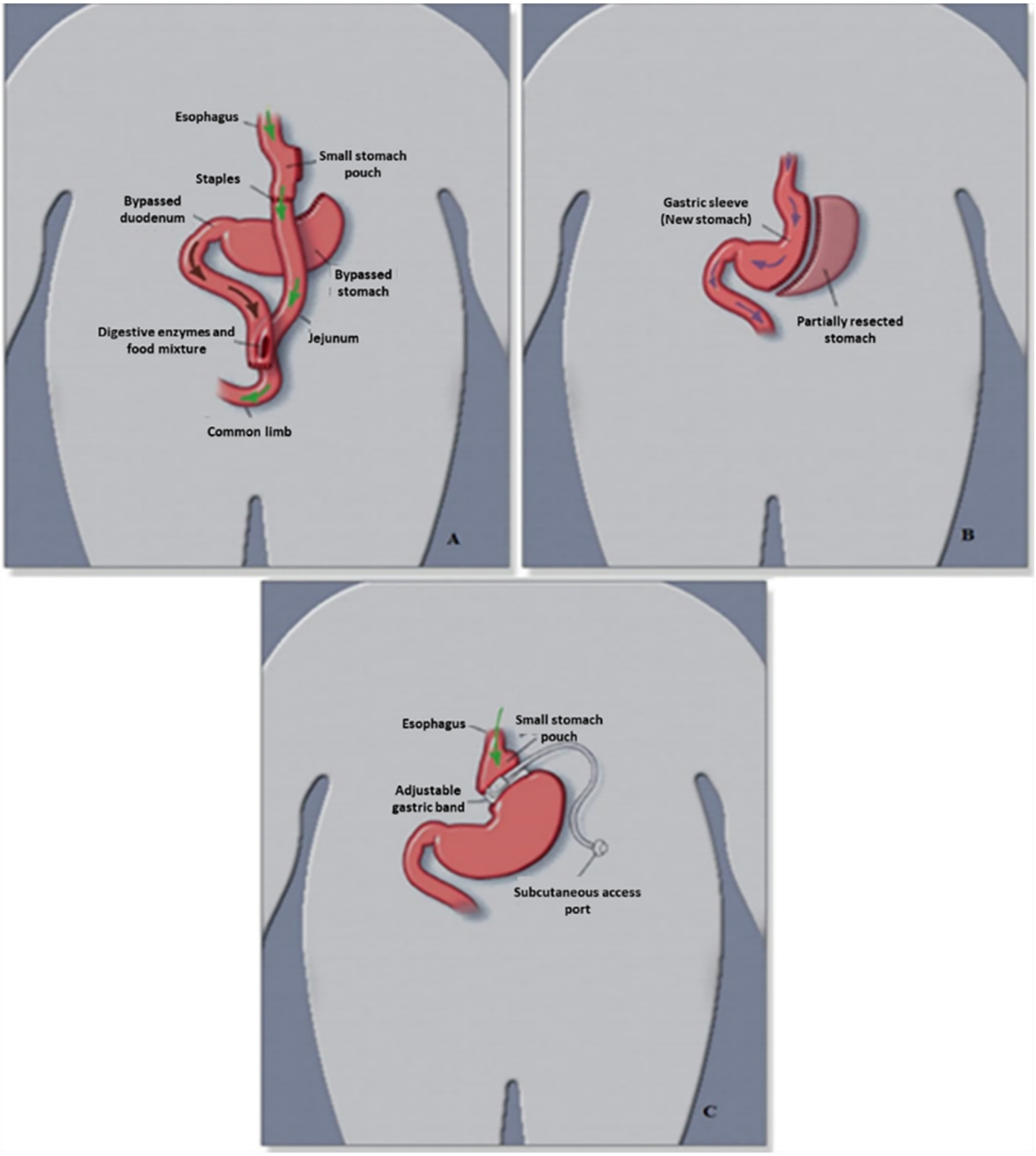

Fig. 1. BS types; RYGB (A), Sleeve (B), and AGB (C).

hunger feeling, increases the energy expenditure, significant long-term weight loss (60–80% of the excess body weight), decreases the amount of food consumed, and preserving 50% of the weight loss during this procedure. However, RYGB has some disadvantages, most critical issue regarding this BS altering the absorption of many medicines and nutrients. (American Society for Metabolic and Bariatric Surgery. Bariatric Surgery Procedures. https://asmbs.org/patients/bariatric-surgery-procedures (accessed Feb 15, 2020).

2.1.1. Jejunoileal bypass (JIB)

JIB was popular in the 1960s and the early 1970s and known to be an efficient way for a significant reduction in body mass. The procedure of JIB was by the induction of surgical short bowel syndrome, through attaching a 35 cm the jejunum to 10 cm of the ileum. JIB gave excellent results in reducing weight (patient who weighed 120 Kg would lose up to 57 Kg by the end of the first year), but it has many complications that can be life-threatening, such as acute liver failure. This type of BS is no longer used due to the high-risk levels (Singh et al., 2009).

2.2. Sleeve gastrostomy

Laparoscopic Sleeve Gastrectomy (LSG), which is known as sleeve, is performed by reducing the content of the stomach by 80%, and the rest of the tubular pouch resembles a banana shape as shown in Fig. 1. This procedure does not alter the rout of digesting such that from RYGB and thus has less complication and minor medical care monitoring, concerning the changes of the guts hormones which deplete the appetite and hunger feeling and thus induce a rapid weight loss similar to that of the RYGB (about 50% of the excess body weight), while maintain this loss. Regardless of these advantages, LSG may lead to faster complications and considered non-reversible procedure; subsequently, it also changes the absorption of many medicines and nutrients .(American Society for Metabolic and Bariatric Surgery. Bariatric Surgery Procedures. https://asmbs.org/patients/bariatric-surgery-procedures (accessed Feb 15, 2020).

2.3. Adjustable gastric band (AGB)

Also known as band, which surrounds the upper portion of the stomach with an inflatable band that creates a small pouch above the band, and the rest of the stomach below the band, as shown in Fig. 1. This procedure is considered the safest among other BS, with a minimum rate of complications. Concomitantly, it reduces the excess body weight approximately by 40–50% by inducing the same conditions of RYGB and LGB, requires less monitoring and medical care, is considered reversible and adjustable, and most importantly, involves no cutting or rerouting. Nevertheless, AGB has a significant issue, which is the potential reoperation due to the possibility of some mechanical problems with the band along with the deviations of the absorption of medicines and nutrients. (American Society for Metabolic and Bariatric Surgery. Bariatric Surgery Procedures. https://asmbs.org/patients/bariatric-surgery-procedures (accessed Feb 15, 2020).

Although BS is an effective way to reduce weight and overcome many health complications, however, it interferes with many medications' absorptions and nutrients because of altering the physiological conditions of the gastrointestinal tract.

3. Bariatric surgery altering the absorption of medications

Ever since WHO declared that obesity is a global epidemic disease which endanger the future of population health status; patients who are susceptible to induce further complications such; Diabetes type II, and cardiovascular diseases and patients with such conditions, that struggled to lose weight through the conventional ways (pharmacotherapy, and lifestyle modifications) started to search for fast and reliable procedure to reduce weight and maintaining this loss. BS was found to be the most efficient and rapid weight loss procedure, which does not require altering the lifestyle and excessive exercises that some patients are not able to perform, and thus, became one of the most common and targeted ways to overcome weight problems. In addition to that, many physicians recommended BS to be a part of therapy for patients with some diseases like diabetes Type II. Nonetheless, many reports had concluded that BS had changed many medicines and nutrients absorption, which led to malnutrition and uncontrolled therapeutics outcomes. Table 1 briefly summaries some of the deviations in the absorption of drugs and nutrients based on published reports and reviews (Padwal et al., 2009).

Niward et al. (2018), evaluated the deviation of rifampicin plasma concentration and its effect on the therapeutic outcome of the treatment. The authors had acknowledged the activity of the anti-tubeless drug as tuberculosis drug activity and correlate the effect of Rifampicin to tuberculosis drug activity as an analytical method to monitor the therapy of tuberculosis. That study concluded that low plasma concentration of Rifampicin resulted in a significant low tuberculosis drug activity level, and thus, the clinical progression of the infection (Niward et al., 2018).

Metformin high plasma concentration would cause the drug to reach its toxicity level. According to Suchard et al. (2008), Metformin toxicity is associated with lactic acidosis that may result in high-level glucose (Hyperglycemia), which may be a consequence of pancreatitis and furthermore risk on patient life (Suchard et al., 2008). Regarding BS, Metformin concentration is increased due to the enhanced bioavailability that follows the surgery, which may be a reason for further complications and eventually compromising the therapy option.

Azithromycin is an antibacterial drug classified as macrolide. With an insufficient level of Azithromycin in plasma, the minimum inhibitory concentration (MIC) of the drug would not be attained, and thus resistance is a possible consequence. According to Jensen et al., 2008, the failure of Azithromycin treatment can be the cause of mutation in the region V of the 13S rRNA gene, which is the leading site of mollicutes (class of bacteria lacks a cell wall); that is inhibited by macrolides (Jensen et al., 2008). BS is known for reducing the bioavailability of Azithromycin which incorporate to reduces the plasma concentration and furthermore the possibility to induce a resistance for Azithromycin. In this case dose must be adjusted and therapy regimen must be reconsidered.

Table 1
Drugs affected by BS.

Drug	Type of BS	Absorption	Reference
Omeprazole	RYGB	Faster	Tandra et al., 2013
Ampicillin	JIB	Decreased	Kampmann et al., 1984
Cyclosporine A	JIB	Decreased	Chenhsu et al., 2003
Tacrolimus	RYGB	Decreased	Rogers et al., 2008
Levothyroxine	RYGB	Delayed	Rubio et al., 2012
Hydrochlorothiazide	JIB	Decreased	Backman et al., 1979
Digoxin	RYGB	Increased	Chan et al., 2015
Phenytoin	RYGB	Decreased	Pournaras et al., 2011
Azithromycin	RYGB	Decreased	Padwal et al., 2012
Escitalopram	RYGB	Decreased	Svetkey et al., 2008
Metformin	RYGB	Increased	Padwal et al., 2011
Tolbutamide	RYGB	Faster	Tandra et al., 2013
Dextromethorphan	RYGB	Faster	Tandra et al., 2013
Atorvastatin	RYGB	Increased	Skottheim et al., 2009

Dramatically, BS is considered a critical bioavailability influencer for the changes that it provides to the physiology of patients' bodies.

4. BS mutates the physiology of the stomach and duodenum

The stomach is located in the upper left part of the abdominal cavity (pH 1–3). It is responsible for receiving the content of the esophagus, process this content (digestion, absorption, and defense against microbes), and finally empties its content into the duodenum. Stomach is divided into 4 main parts: the cardia, fundus, body, and pylorus (Fig. 2). The cardia is the first part of the stomach under the esophagus, which prevents the content from reflexing to the esophagus from the stomach. The fundus is the upper right part of the stomach, right under the diaphragm, which is responsible for storing the undigested food and chyme (Kiela and Ghishan, 2016). The body is the largest part of the stomach that contains the antrum (where the digested food is located and being prepared to leave the stomach). This where the mixing and digestion of food are processed, it also has the responsible cells for the secretion of gastric enzymes, such as "Chief Cell," which is responsible for the secretion of Pepsin. Finally, the pylorus is the part where food leaves the stomach into the small intestines through the pylorus sphincter, which is also responsible for preventing the contents of the small intestines to go back to stomach (Kiela and Ghishan, 2016).

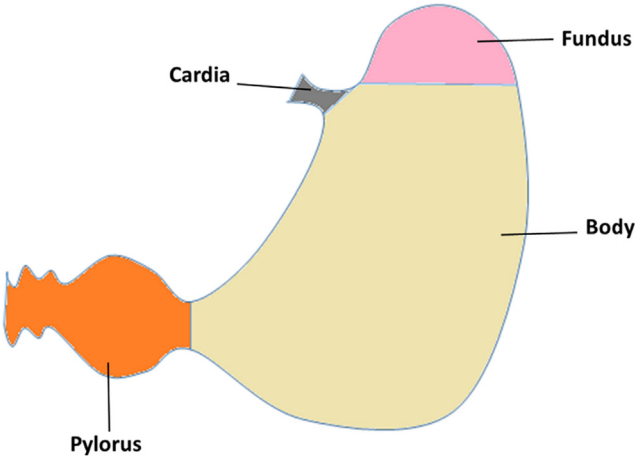

Fig. 2. Stomach parts.

The primary function of the stomach is digestion, which is defined as the process of mechanically, and chemically degradation of food into small particles mixed with gastric enzymes (Chyme), which can be furthermore absorbed into the blood circulatory. Food that undergoes digestion is divided into three main classes: fats, carbohydrates, and proteins. Regarding the mechanical digestion, it can be introduced in the oral cavity by chewing or mastication, and in the stomach, that contains three layers of smooth muscles by the process of churning (Kiela and Ghishan, 2016). On the other hand, chemical digestion depends on the gastric enzymes and hormones; the gastric enzymes include Pepsin and gastric lipase, while gastric hormones include; Hydrochloric acid, Intrinsic factor (IF), Mucin, and gastrin (Kiela and Ghishan, 2016).

Concerning oral Drug Delivery System DDS, the stomach plays an essential role for absorption, as it stands for the process of dissolution of tablets and capsules, which prepare the drug particles to be transported to the bloodstream. Some drugs have basic nature that needs the acidic medium of the stomach to be dissolved; these drugs would precipitate in the absence of the stomach due the basic nature of the intestines (for example, cinnarizine) (Shahba et al., 2012). Regardless of the role of digestion, stomach is considered a site of absorption of certain drugs, such as aspirin (Gupta and Singh, 2012), that BS would result in the ineffectiveness of the medicine due to the lack of absorption site (Gupta and Singh, 2012). Moreover, IF is an essential glycoprotein for vitamin B12 absorption, as it has a unique receptor at the ileum that facilitates the translocation of vitamin B12 into the circulatory system (Gupta and Singh, 2012).

Duodenum, Fig. 3, is the first part of the small intestines that is 25–38 cm in length in humans. It plays a vital role in the chemical degradation of food into smaller sizes and regulates the rate of

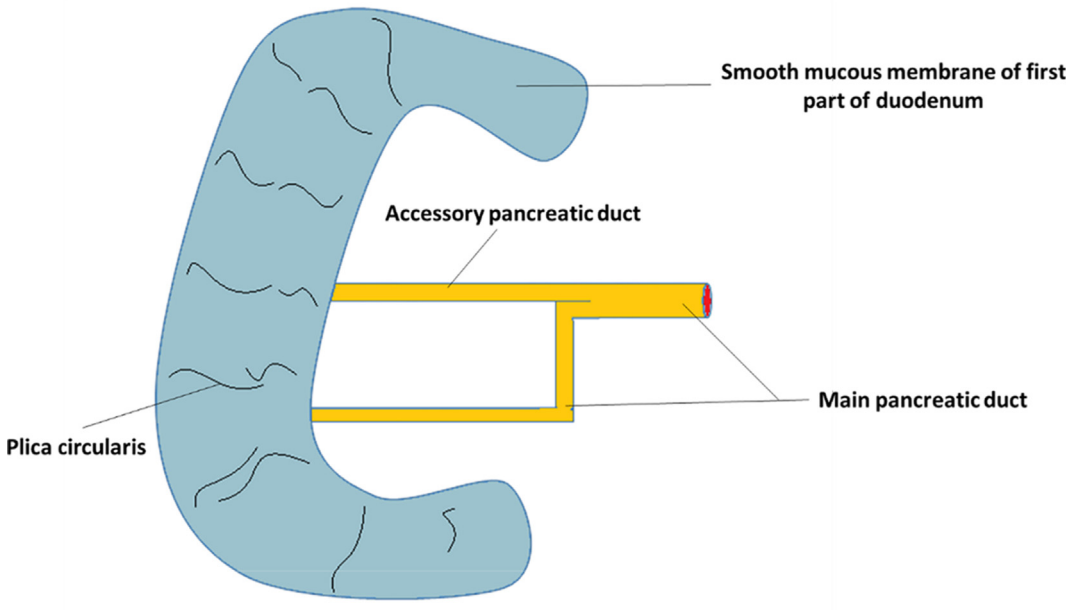

Fig. 3. Duodenum, and the pancreatic duct.

emptying of the stomach through two main hormones; secretin and cholecystokinin (Gupta and Singh, 2012).

Duodenum is considered the primary site of alkalizations that shifts the pH from 2 to 7 to avoid the damage of intestinal mucosa. It also found to be amino acids site of absorption for many elements such as calcium and iron. Regarding nutrients absorption and digestion, duodenum helps to start the starch hydrolysis, protein digestion, and fat absorption. The pancreatic duct delivers alpha-amylase that hydrolysis carbohydrates and prepares it to be absorbed. Additionally, protein reaches the duodenum in the form of cleaved chains of amino acid, which by the secretion of pancreatic endopeptidase (enterokinase), convert trypsinogen into its active form trypsin that helps in digest amino acids and absorb it. Furthermore, most of the lipids are absorbed in the duodenum; cholecystokinin is secreted in the presence of fat in the duodenum, which stimulates the secretion of pancreatic lipase that is responsible for the hydrolysis of dietary lipids. The Bile acids are secreted into the duodenum through the bile duct, which is responsible for the emulsification of the fat and thus yielding micelles and liposomes, which in turn may passively diffuse into the bloodstream via the fatty acid transport proteins (Gupta and Singh, 2012).

The most common BS is the RYGB, which indicates the removal of the Stomach and duodenum with some parts of the jejunum. Concomitantly, these resected parts are essential for the absorption of drugs and nutrients, whether absorptions physically occur, or drugs demand the digestion process of these parts to be absorbed. For example, Vitamin D3 is a fat-soluble vitamin that is absorbed by duodenum; it was found that after RYGB, the bioavailability of vitamin D3 dropped down by 25% (Aarts et al., 2011). Bypassing the stomach and duodenum causes the lack of essential enzymes that are crucial for the process of absorption of drugs and nutrients; this triggers the urge for a drug delivery system that can overcome this crisis and replace the deviated enzymes.

5. Bioavailability

According to the Code of Federal Regulations (CFR 21.320.1) in the USA, Bioavailability is the rate and extent (fraction or the percentage of the dose) to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action (Löbenberg and Amidon, 2000). However, it is difficult to measure the drug concentration directly at the site of action; thus most bioavailability studies involve the measurement of drug concentration in blood. This is based on the premise that the drug at the site of action is in equilibrium with the drug in the blood. Committee for Proprietary Medicinal Products of the European Medicines Evaluation Agency extends the above definition by adding the sentence, "Bioavailability is understood to be the extent and the rate to which a substance or its therapeutic moiety is delivered from a pharmaceutical form into the general circulation." This additional sentence, including systemic clearance variation in the definition, is more restrictive (Löbenberg and Amidon, 2000). Clinically, Bioavailability is an essential issue because pharmacologic and toxic effects are proportional to both dose and bioavailability (Aungst, 1993).

BS had shown that it affects the bioavailability of drugs. In 1991, Gubbins et al. discussed the effect of GIT surgeries on the absorption of drugs and categorized the resultant malabsorption in three main reasons; reducing the surface area of the intestines, altering the gastric emptying time, and changing the pH (Gubbins and Bertch, 1991). Rogers et al. evaluated the effect of the pharmacokinetics of tacrolimus and sirolimus after gastric bypass surgery in end-stage renal disease and transplant patients. The study indicates the reduction of absorption for tacrolimus and sirolimus due to the bypassing of their primary absorption site (Duodenum), it also showed that P-gp substrates and P-450 (Cytochrome) 3A4/5 metabolic drugs bioavailability would be affected by BS (Rogers et al., 2008). This proves that oral medication absorption is altered due to the BS. However, Bioavailability can be restored by delivering the auspicious shifting of the drug from the absorption site to the circulatory system.

The successful transposition of a drug from an oral dosage form into the general circulation can be described as a four-step process:

1. Disintegration of the drug product (if the drug product is solid).
2. Dissolution of the drug in the fluids at the absorption site.
3. Movement of the dissolved drug through the membranes of the GI Tract.
4. Movement of the drug away from the site of absorption into the general circulation.?

The introduction of the Biopharmaceutical Classification System (BCS) in FDA guidelines represents a significant step forward in the regulation of oral drug products. The guidelines classify drug substances into four categories according to their permeability and solubility properties. Class I is highly soluble and permeable, while Class IV is poorly soluble and permeable. Drugs belongs to Class II are poorly soluble and highly permeable and Class III are highly soluble and poorly permeable.

Knowledge of BCS help the formulation scientists to develop a dosage form based on mechanistic, rather than empirical, approaches. The BCS groups poorly soluble compounds as Class II and IV drugs, feature poor solubility and high permeability, and poor solubility and poor permeability, respectively. Drug substances are considered highly soluble when the largest dose of a compound is soluble in <250 mL water over a range of pH from 1.0 to 7.5; highly permeable compounds are classified as those compounds that demonstrate >90 percent absorption of the administered dose (Gubbins and Bertch, 1991; Rogers et al., 2008). In contrast, compounds with solubility below 0.1 mg/mL face significant solubilization obstacles, and often, even compounds with solubility below 10 mg/mL present difficulties related to solubilisation during formulation. Class I drugs do not pose any problem in absorption (though its systemic availability may be low due to first pass metabolism) when solubility or permeability are considered, therefore efforts are made to change the properties of Class II, III, IV drugs with respect to dissolution and permeability to resemble Class I shows the possibilities of shifting the solubility-dissolution characteristics of Class II, III, and IV drug to resemble Class I features.

6. Advanced drug delivery systems (DDS) to enhance bioavailability

There is a full agreement among healthcare professionals and patients that the oral route of administration is the commonly used and preferred drug delivery system (Mohsin et al., 2009). This preference is due to several strong reasons such as ease of administration by the patients themselves, high patient compliance, cost-effectiveness, and least sterility constraints for such dosage forms are required from the manufacturers (Mohsin, 2012). However, a significant problem of administration via the oral route is the poor bioavailability of some drugs and most of the new chemical entities. >70% of these new entities and the marketed drugs have poor bioavailability, which is caused by their poor aqueous solubility and dissolution (class II: BCS) (Mohsin, 2012; Mohsin and Pouton, 2012). Clinically, the poor bioavailability of the drug could result in many drawbacks, such as the least therapeutic benefit and insufficient clinical outcome. Accordingly, these problems create a significant challenge in formulating these drugs into oral medications with sufficient bioavailability (Dahan and Hoffman, 2008).

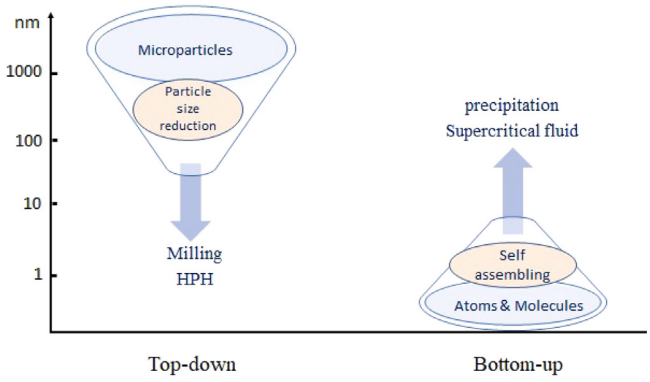

Fig. 4. Types of nanotechnology processes.

Collectively, BS reduces the absorption of drugs, regardless to its classifications, and most of the drugs are considered poor water-soluble drugs (Dahan and Hoffman, 2008), this leads to an urgent search for DDS that can overcome these drawbacks. Recently, nanotechnology (Fig. 4) has been used to enhance bioavailability through increasing the surface area and dissolution of the absorption site by controlling the shape and size of the particles at nano range (particle size < 1000 nm) which are intended to be absorbed, this technique provides an enhanced physicochemical and biopharmaceutical properties. Nanonization includes; Nanocrystals and Nanosuspension.

Nanocrystals are a submicron colloidal drug delivery system that exists as a combination of the pure drug and small amount of surfactant to be stabilized with a size less than 800 nm. Many advantages lie behind nanocrystals such as; high dissolution rate, possibility to be administered in the different routes of administration, the flexibility in designing different pharmaceutical dosage forms, enhanced solubility, and potential for passive targeting drugs. On the other side, nanocrystals show few disadvantages; such as, stability problems due to its physicochemical properties, also, the difficulty in achieving nanocrystals in accurately uniform state (Gigliobianco, 2018).

Regarding nanosuspension, it's a colloidal dispersion with a size range of 200–700 nm (Zhang et al., 2011), which is stabilized by surface-active agents. Nanosuspensions hold many advantages along with advantages of nanocrystals, such as; it enhances the solubility of poorly water-soluble drugs in aqueous media as well as lipid media, high plasma concentration level in a short time, it's a liquid formulation which makes it susceptible to be administered by parenteral route only if the size is reduced to minimum to avoid any blockage in the blood capillary. It can be lyophilized into a solid matrix. Nevertheless, nanosuspension hides some cons, due to its bulkiness, it is hard to be handled, extra care required, physically unstable (sedimentation and compaction may be an issue), dose uniformity cannot be achieved unless the particles are suspended. One of the nanosuspension preparation techniques is the nanoemulsion, which is widely used in enhancing the bioavailability of poorly water-soluble drugs by creating an isocratic mixture containing; oil, surfactant, cosurfactants, and the drug. This technique is known to provide some small size particles (particles < 200 nm) that would increase the dissolution area and thus better bioavailability (Patel and Agrawal, 2011).

Nanonization of the particles can be obtained via two main processes: Top-Down and Bottom-Up technologies (Sunder and Nair, 2016).

6.1. Top-down technology in DDS

This technique includes; milling and high-pressure homogenization. These methods are used to reduce the particle size of the drugs to control enhance the surface area and thus obtain a better dissolution, which may result in better absorption and bioavailability. Milling (also known as size reduction, comminution, grinding, and pulverization) is the use of mechanical energy to break down coarse particles into smaller ones (fine particles) regardless of its solubility in aqueous or non-aqueous solvents (Lakshmi and Kumar, 2010).

Milling is utilized by reducing the size of the active ingredient to improve its bulk properties. After achieving the desired size, the resultant particles are furthermore added to other excipients to reach an optimized formulation with better physicochemical properties. Planetary ball mill, which uses Zirconium balls with different sizes to produce the intended particle sizes are considered one of the most utilized methods of milling lately. Alshora et al. (2018), had studied the ability of planetary ball mill in enhancing the dissolution and bioavailability of poorly water-soluble drugs rosuvastatin administered through the oral route, the intended particle size for the study was less than 800 nm, and the leading formula obtained resulted in particle with a size of 461.8 ± 16.68 nm (Alshora et al., 2018). The study concluded that using this technique had improved the surface area of the particles and thus enhance the *in Vitro* dissolution of the rosuvastatin significantly to its reference. Moreover, the *Vivo* supported the ability of this process to increase the plasma concentration of the drug as it was substantially higher than that of the raw drug. This result concluded that reducing the size of the particles would result in better dissolution and thus enhanced bioavailability (Alshora et al., 2018, 2019). These results can be promising in case of BS as it proofs that reducing the size of the drug is directly contributed to enhanced bioavailability of the drugs. Reducing the particle size improves the surface area which in return expose larger amount of the drug to the dissolution medium and make the drug ready to be absorbed.

On the other hand, high-pressure homogenization, the drug is involved in a suspension which under pressure is forced through a valve having a narrow aperture. This technique aims to decreases the static pressure below the boiling point of water at room temperature by increasing the pressure of the fluid at the homogenization gap; this would lead to the formation of air bubbles which eventually leaves the go off when the suspension escapes the gap (cavitation), and as a consequence, normal air pressure is attained again. The resultant forces are mainly responsible for the collision of the particles and thus impulsiveness breakdown of the drug to Nano-size particles (Keck and Muller, 2006).

Gora et al. (2016), Drug nanocrystals of poorly soluble drugs produced by high pressure homogenization evaluated the ability of high-pressure homogenization in enhancing the dissolution and the pharmacokinetics/pharmacodynamics properties of the poorly water-soluble drugs valsartan. The optimized formula had Nano-sized particles, which was furthermore compared to a physical mixture of the crude drug and excipients. The outcome of the studied showed that the optimized formula had a significant impact on increasing the dissolution and plasma concentration of valsartan, which concomitantly transcript to better drug effect to its compared drug (Gora et al., 2016).

6.2. Bottom-Up technology in DDS

This technique holds excellent advantages against Top-Down technique as it does not require the consumption of energy and thus is more suitable for drugs with sensitivity toward heat or mechanical stress. In addition to that, it requires simple instruments with a low cost of production. This method of preparation had been widely used in the pharmaceutical industry for its convenient results and ease of use (Sinha et al., 2013). This process is commonly called precipitation due to the main target of its' use,

which is precipitating the drug particles from a supersaturated solution of the drug, which in return produces a narrow size distribution of the particle not like that of other techniques (Rasenack and Müller, 2004). A supersaturated solution is defined as the process when the solution containing more solute that exceeds its saturation limit, in case of pharmaceutical drug delivery systems, the solute is the drug, and the solvent is the media that dissolves the drug (aqueous or nonaqueous). Advanced techniques are available such as; supercritical fluid (SCF) and selfnanoemulsifying drug delivery system (SNEDDS) (Hou et al., 2019, Bahloul et al., 2015, Al-fagih et al., 2011).

Hou et al. (2019), investigated the ability of SCF in preparing self-assembled micelles of the Geranium macrorrhizum extract, Germacrone (class II in BCS), which expected to enhance the solubility and thus bioavailability of the extract (Hou et al., 2019). The authors used an improved supercritical reverse phase evaporation (ISCRPE) method in developing a unilamellar liposome which has high encapsulation efficiency and stability due to the avoidance of the organic solvents in this technique. The study concluded that the developed formula using ISCRPE had better bioavailability, stability, and high encapsulation efficiency compared to free germacroene (Hou et al., 2019).

6.2.1. Selfnanoemulsifying drug delivery system (SNEDDS)

Among the varies techniques of lipid-based formulations used in enhancing the bioavailability of drugs, whether it is considered water-soluble or poorly water-soluble drugs, SNEDDS are considered a promising technique that showed better stability, ease of preparation, dose flexibility, enhanced solubility, and most importantly better bioavailability.

SNEDDS represents one of the most potential candidates in terms of improving the in-vivo performance of orally delivered poorly water-soluble drugs (Bahloul et al., 2015). SNEDDS are isotropic mixtures of oil, surfactant, and drug entity with cosurfactant or cosolvent. They have a unique property; upon aqueous dilution (as such in GIT fluids) followed by mild agitation, these systems can form oil-in-water nanoemulsions. Upon oral administration, SNEDDS spread spontaneously in the GIT, and its digestive motility provides the necessary agitation required for self-emulsification (Gursoy and Benita, 2004- Date et al., 2010). Compared with other drug delivery systems, SNEDDS offers valuable advantages such as ease of manufacture and scale-up, better physical stability, and enhanced drug entrapment capacity. Many of the utilized excipients are food-grade materials and categorized as GRAS (Generally Recognized as Safe). Therefore, they do not present a toxicological risk to the formulator or the patient (Gursoy and Benita, 2004; Date et al., 2010). One of the vital benefits of SNEDDS over other drug delivery systems is the prevention of the physical instability problem occurring with nanoparticles, nanoemulsions, and liposomes (Gursoy and Benita, 2004). Due to their nano-size, SNEDDS is expected to self-emulsify rapidly in the GIT aqueous contents. Hence, no dissolution step would be required due to the spontaneous nanoemulsion formation (Mohsin et al., 2012; Pouton, 2000). These nano-droplets would be emptied rapidly from the stomach resulting in faster drug release all over the GIT. A further advantage of SNEDDS, compared to a simple oily solution, is producing much larger interfacial area for the partitioning of the drug between oil and water, leading to enhanced solubilization. Contrary to oily solutions, SNEDDS doesn't depend on the action of enzymes, bile salts, and/or other food-related effects (Balakumar et al, 2013). This leads to a greater absorption rate/extent and, therefore, higher and more reproducible bioavailability values (Balakumar et al, 2013; Gupta at al., 2013).

Chen et al. (2019), prepared SNEDDS of silymarin and in-vivo study was performed on RYGB rats. the pharmacokinetics results showed significant enhancement in both C_{max} and AUC compared with suspension forms. The C_{max} and AUC of silymarin increased by 2.5-fold from SNEDDS compared to silymarin suspension (Chen et al., 2015).

7. Conclusion

Obesity is an epidemic disease that is rapidly distributed throughout the world and among all ages. Treatment options of obesity are varying, and among these options, BS ~~is~~ that considered the most reliable and recommended by physicians. However, BS is the best treatment choice, but it holds a major problem between its pages. Altering the absorption and the bioavailability of medication may lead to severe complications that threaten the life of the patients. Pharmaceutical formulators had been using nanotechnology to improve the bioavailability of class II drugs that have problems in dissolutions and bioavailability. Nanotechnology is a promising technique to be used to solve the BS malabsorption problem. Future studies are a must in the field of understanding the mechanism of action for drug malabsorption by BS, along with investigating a suitable drug delivery system that holds promising outcomes for improving the bioavailability of influenced drugs.

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References

Aarts, E., van Groningen, L., Horst, R., Telting, D., van Sorge, A., Janssen, I., de Boer, H., 2011. Vitamin D absorption: consequences of gastric bypass surgery. Eur. J. Endocrinol. 164 (5), 827–832. https://doi.org/10.1530/EJE-10-1126.

Alqarni, S.S., 2016. A review of prevalence of obesity in Saudi Arabia. J. Obes. Eat Disord. 2 (2). https://doi.org/10.21767/2471-8203.100025.

Al-fagih, I.M., Alanazi, F.K., Hutcheon, G.A., Saleem, I.Y., 2011. Recent advances using supercritical fluid techniques for pulmonary administration of macromolecules via dry powder formulations. Drug Deliv. Lett. 1 (2), 128–134.

Al-Quwaidhi, A.J., Pearce, M.S., Critchley, J.A., Sobngwi, E., O'Flaherty, M., 2014. Trends and future projections of the prevalence of adult obesity in Saudi Arabia, 1992–2022. Eastern Mediterranean Health J. 20 (10) http://applications.emro.who.int/emhj/v20/10/EMHJ_2014_20_10_589_595.pdf.

Alshora, D.H., Ibrahim, M.A., Elzayat, E., Almeanazel, O.T., Alanazi, F., 2018. Rosuvastatin calcium nanoparticles: Improving bioavailability by formulation and stabilization codesign. PLoS ONE 13, (7). https://doi.org/10.1371/journal.pone.0200218 e0200218.

Alshora, D., Ibrahim, M., Elzayat, E., Almeanazel, O.T., Alanazi, F., 2019. Defining the process parameters affecting the fabrication of rosuvastatin calcium nanoparticles by planetary ball mill. Int. J. Nanomed. 14, 4625. https://doi.org/10.2147/IJN.S207301.

Arterburn, D.E., Olsen, M.K., Smith, V.A., Livingston, E.H., Van Scoyoc, L., Yancy, W.S., et al., 2015. Association between bariatric surgery and long-term survival. JAMA 313 (1), 62–70. https://doi.org/10.1001/jama.2014.16968.

Aungst, B.J., 1993. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. J. Pharm. Sci. 82 (10), 979–987. https://doi.org/10.1002/jps.2600821008.

Backman, L., Beermann, B., Groschinsky-Grind, M., Hallberg, D., 1979. Malabsorption of hydrochlorothiazide following intestinal shunt surgery. Clin. Pharmacokinet. 4 (1), 63–68. https://doi.org/10.2165/00003088-197904010-00006.

Bahloul, B., Lassoued, M.A., Seguin, J., Lai-Kuen, R., Dhotel, H., Sfar, S., Mignet, N., 2015. Self-emulsifying drug delivery system developed by the HLB-RSM approach: characterization by transmission electron microscopy and pharmacokinetic study. Int. J. Pharm. 487 (1–2), 56–63. https://doi.org/10.1016/j.ijpharm.2015.04.018.

Balakumar, K., Raghavan, C.V., Abdu, S., 2013. Self nanoemulsifying drug delivery system (SNEDDS) of rosuvastatin calcium: design, formulation, bioavailability and pharmacokinetic evaluation. Colloids Surf., B 112, 337–343. https://doi.org/10.1016/j.colsurfb.2013.08.025.

Buchwald, H., Oien, D.M., 2009. Metabolic/bariatric surgery worldwide 2008. Obes. Surg. 19 (12), 1605–1611. https://doi.org/10.1007/s11695-009-0014-5.

Buchwald, H., Williams, S.E., 2004. Bariatric surgery worldwide 2003. Obes. Surg. 14 (9), 1157–1164. https://doi.org/10.1381/0960892042387057.

Centers for Disease Control and Prevention. Overweight and obesity. https://www.cdc.gov/obesity/index.html. (accessed Feb-15, 2020).

Chan, L.N., Lin, Y.S., Tay-Sontheimer, J.C., et al., 2015. Proximal Rouxen-Y gastric bypass alters drug absorption pattern but not systemic exposure of CYP3A4 and P-glycoprotein substrates. Pharmacotherapy 35, 361–369.
Chen, C.H., Chang, C.C., Shih, T.H., Aljuffali, I.A., Yeh, T.S., Fang, J.Y., 2015. Self-nanoemulsifying drug delivery systems ameliorate the oral delivery of silymarin in rats with Roux-en-Y gastric bypass surgery. Int. J. Nanomed. 10, 2403–2416.
Chenhsu, Y., Wu, Y., Katz, D., Rayhill, S., 2003. Dose-adjusted cyclosporine c2 in a patient with jejunoileal bypass as compared to seven other liver transplant recipients. Ther. Drug Monit. 25, 665–670.
Christou, N.V., Sampalis, J.S., Liberman, M., Look, D., Auger, S., McLean, A.P., MacLean, L.D., 2004. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. Ann. Surg. 240 (3), 416–424.
Dahan, A., Hoffman, A., 2008. Rationalizing the selection of oral lipid based drug delivery systems by an in vitro dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs. J. Control. Release 129 (1), 1–10.
Date, A.A. et al., 2010. Self-nanoemulsifying drug delivery systems: formulation insights, applications and advances. Nanomedicine (Lond) 5 (10), 1595–1616.
do Carmo, J.M., da Silva, A.A., Wang, Z., Fang, T., Aberdein, N., de Lara, Rodriguez, C.E. P., et al., 2016. Obesity-induced hypertension: brain signaling pathways. Curr. Hypertens. Rep. 1(1), 18–58.
Gigliobianco, R., Casadidio, C., Censi, R., et al., 2018. Nanocrystals of poorly soluble drugs: drug bioavailability and physicochemical stability. Pharmaceutics 10 (3), 134.
Gora, S., Mustafa, G., Sahni, J.K., Javed Ali, J., Baboota, S., 2016. Nanosizing of valsartan by high pressure homogenization to produce dissolution enhanced nanosuspension: pharmacokinetics and pharmacodyanamic study. Drug Deliv. 23 (3), 930–940.
Grundy, S.M., Barnett, J.P., 1990. Metabolic and health complications of obesity. Dis. Mon. 36, 641–731.
Gubbins, O., Bertch, E., 1991. Drug absorption in gastrointestinal disease and surgery. Clin. Pharmacokinet. 21 (6), 431–447.
Gupta, G., Singh, A., 2012. A short review on stomach specific drug delivery system. Int. J. PharmTech Res 4 (4), 1527–1545.
Gupta, S., Kesarla, R., Omri, A., 2013. Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems. ISRN Pharm. 2013, 16.
Gursoy, R.N., Benita, S., 2004. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed. Pharmacother. 58 (3), 173–182.
Hou, X., Cao, B., He, Y., et al., 2019. Improved self-assembled micelles based on supercritical fluid technology as a novel oral delivery system for enhancing germacrone oral bioavailability. Int. J. Pharm. 569 (118586), 1–10.
Jensen, J., Bradshaw, C., Tabrizi, S., et al., 2008. Azithromycin treatment failure in mycoplasma genitalium–positive patients with nongonococcal urethritis is associated with induced macrolide resistance. Clin. Infect. Dis. 47 (12), 1546–1553.
Kampmann, J.P., Klein, H., Lumholtz, B., Molholm Hansen, J.E., 1984. Ampicillin and propylthiouracil pharmacokinetics in intestinal bypass patients followed up to a year after operation. Clin. Pharmacokinet. 9, 168–176.
Karmali, S., Stoklossa, J., Sharma, A., et al., 2010. Bariatric surgery: a primer. Can. Fam. Physician 56 (9), 873–879.
Keck, C.M., Müller, R.H., 2006. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur. J. Pharm. Biopharm. 62 (1), 3–16. https://doi.org/10.1016/j.ejpb.2005.05.009.
Kenchaiah, S., Evans, J.C., Levy, D., Wilson, P.W.F., Benjamin, E.J., Larson, M.G., et al., 2002. Obesity and the risk of heart failure. N. Engl. J. Med. 347, 305–313.
Kiela, P.R., Ghishan, F.K., 2016. Physiology of intestinal absorption and secretion. Best Pract. Res. Clin. Gastroenterol. 30 (2), 145–159.
Lakshmi, P., Kumar, G., 2010. Nanosuspension technology: a review. Int. J. Pharm. Pharm. Sci. 2 (4), 35–40.
Löbenberg, R., Amidon, L., 2000. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. Eur. J. Pharm. Biopharm. 50 (1), 3–12.
Mahmood, A., Arulkumaran, S., 2013. Obesity: a ticking time bomb for reproductive health. J. Obesity Eating Disorder 1 (1).
Mohsin, K., Shahba, A., Alanazi, F.K., 2012. Lipid based self emulsifying formulations for poorly water soluble drugs-an excellent opportunity. Indian J. Pharm. Educat. Res. 46 (2), 88–96.
Mohsin, K., 2012. Design of lipid-based formulations for oral administration of poorly water-soluble drug fenofibrate: effects of digestion. AAPS PharmSciTech 13 (2), 637–646.
Mohsin, K., Long, M.A., Pouton, C.W., 2009. Design of lipid-based formulations for oral administration of poorly water-soluble drugs: precipitation of drug after dispersion of formulations in aqueous solution. J. Pharm. Sci. 98 (10), 3582–3595.
Mohsin, K., Pouton, C.W., 2012. The influence of the ratio of lipid to surfactant and the presence of cosolvent on phase behaviour during aqueous dilution of lipid-based drug delivery systems. J. Drug Del. Sci. Tech. 22 (6), 531–540.
Nguyen, T., Nguyen, T., Lane, J., et al., 2011. Relationship between obesity and diabetes in a US adult population: findings from the national health and nutrition examination survey, 1999–2006. J. Obesity Surg. 21 (1), 351–355.
Niward, K., Blom, L., Forsman, L., et al., 2018. Plasma levels of rifampin correlate with the tuberculosis drug activity assay. Antimicrob. Agents Chemother. 62 (5), 1–4.
Nordestgaard, B.G., Palmer, T.M., Benn, M., Zacho, J., TybjærgHansen, A., Smith, G.D., et al., 2012. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a Mendelian randomisation approach. PLoS Med. 9, e1001212.
Padwal, R., Brocks, Sharma, M., 2009. A systematic review of drug absorption following bariatric surgery and its theoretical implications. Obesity Rev. 11 (1), 41–50.
Padwal, R.S., Ben-Eltriki, M., Wang, X., et al., 2012. Effect of gastric bypass surgery on azithromycin oral bioavailability. J. Antimicrob. Chemother. 67, 2203–2206.
Padwal, R.S., Gabr, R.Q., Sharma, A.M., et al., 2011. Effect of gastric bypass surgery on the absorption and bioavailability of metformin. Diabetes Care 34, 1295–1300.
Patel, R., Agrawal, K., 2011. Nanosuspension: an approach to enhance solubility of drugs. J. Adv. Pharm. Technol. Res. 2 (2), 81.
Peckmezian, T., Hay, P., 2017. A systematic review and narrative synthesis of interventions for uncomplicated obesity: weight loss, well-being, and impact on eating disorders. J. Eating Disorders 1 (1), 15.
Pournaras, D.J., Footitt, D., Mahon, D., Welbourn, R., 2011. Reduced phenytoin levels in an epileptic patient following Roux-En-Y gastric bypass for obesity. Obes. Surg. 21, 684–685.
Pouton, C.W., 2000. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'selfmicroemulsifying' drug delivery systems. Eur. J. Pharm. Sci. 11 (Suppl 2), S93–S98.
Rasenack, Norbert, Müller, Bernd W., 2004. Micron size drug particles: common and novel micronization techniques. Pharm. Dev. Technol. 9 (1), 1–13.
Rogers, CC, Alloway, RR, Alexander, JW, CardiM, Trofe, J, Vinks, AA, 2008. Pharmacokinetics of mycophenolic acid, tacrolimus and sirolimus after gastric bypass surgery in end-stage renal disease and transplant patients: a pilot study. Clin Transplant 22, 281–291.
Rogers, C.C., Alloway, R.R., Alexander, J.W., Trofe, J., Cardi, M., Vinks, A.A., 2008. Pharmacokinetics of mycophenolic acid, tacrolimus and sirolimus after gastric bypass surgery in end-stage renal disease and transplant patients: a pilot study. Clin. Transplant. 22, 281–291.
Rubio, I.G., Galrao, A.L., Santo, M.A., Zanini, A.C., Medeiros-Neto, G., 2012. Levothyroxine absorption in morbidly obese patients before and after Roux-En-Y gastric bypass (RYGB) surgery. Obes. Surg. 22, 253–258.
Schauer, R., Bhatt, L., Kirwan, P., et al., 2014. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. N. Engl. J. Med. 370 (21), 2002–2013.
Shahba, A.A.-W., Mohsin, K., Alanazi, F.K., 2012. Novel self-nanoemulsifying drug delivery systems (SNEDDS) for oral delivery of cinnarizine: design, optimization, and in-vitro assessment. AAPS PharmSciTech 13 (3), 967–977.
Sherman, V., 2013. Bariatric surgery. Tex. Heart Inst. J. 40 (3), 296–297.
Simonson, Donald C., Halperin, Florencia, Foster, Kathleen, Vernon, Ashley, Goldfine, Allison B., 2018. Clinical and Patient-Centered Outcomes in Obese Type 2 Diabetes Patients 3 Years After Randomization to Roux-en-Y Gastric Bypass Surgery Versus Intensive Lifestyle Management: The SLIMM-T2D Study. Diabetes Care dc170487. https://doi.org/10.2337/dc17-0487.
Singh, D., Laya, S., Clarkston, K., et al., 2009. Jejunoileal bypass: a surgery of the past and a review of its complications. World J. Gastroenterol. 15 (18), 2277.
Sinha, B., Muller, R., et al., 2013. Bottom-up approaches for preparing drug nanocrystals: Formulations and factors affecting particle size. Int. J. Pharm. 1 (1), 126–141.
Skottheim, I.B., Stormark, K., Christensen, H., et al., 2009. Significantly altered systemic exposure to atorvastatin acid following gastric bypass surgery in morbidly obese patients. Clin. Pharmacol. Ther. 86, 311–318.
Suchard, Jeffrey R., Thomas, A., et al., 2008. Fatal metformin overdose presenting with progressive hyperglycemia. Western J. Emergency Med. 4 (3), 160–164.
Sunder, S., Nair, R., 2016. Methods of nanonization of drugs for enhancing their dissolution. Eur. J. Adv. Eng. Technol. 3 (8), 101–110.
Svetkey, L.P., Stevens, V.J., Brantley, P.J., et al., 2008. Comparison of strategies for sustaining weight loss. JAMA 299, 1139–1148.
Tandra, S., Chalasani, N., Jones, D.R., Mattar, S., Hall, S.D., Vuppalanchi, R., 2013. Pharmacokinetic and pharmacodynamic alterations in the Roux-en-Y gastric bypass recipients. Ann. Surg. 258, 262–269.
Thomas-Valdés, S., Tostes, D., Anunciação, C., et al., 2017. Association between vitamin deficiency and metabolic disorders related to obesity. Critical Rev. Food Sci. Nutr. 5 (15), 3332–3343.
Vanlint, S., 2013. Vitamin D and obesity. Nutrients 5 (3), 949–956.
Zhang, H., Hollis, C.P., Zhang, Q., Li, T., 2011. Preparation and antitumor study of camptothecin nanocrystals. Int. J. Pharm. 415, 293–300.