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Review

Polymeric Carriers for Controlled Drug Delivery in Obesity Treatment

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The global rise in the prevalence of obesity and affiliated metabolic syndrome poses a significant threat to human health. Various approaches, including bariatric surgery and pharmacotherapy, have been used in the clinical setting for obesity treatment; however, these conventional options remain ineffective and carry risks of adverse effects. Therefore, treatments with higher efficacy and specificity are urgently required. Emerging drug delivery systems use polymeric materials and chemical strategies to improve therapeutic efficacy and specificity through stabilization and spatiotemporally controlled release of antiobesity agents. In this review, we provide insights into current treatments for obesity with a focus on recent developments of polymeric carriers for enhanced antiobesity drug delivery.

Highlights

Obesity is the most prevailing chronic disease, affecting 13% of adults worldwide.

There is a critical unmet need for the treatment of obesity.

Conventional obesity treatments often lack efficacy and specificity.

Biodegradable polymeric carriers are designed to achieve spatiotemporally controlled release of small-molecular drugs.

Novel polymeric drug carriers have been shown to overcome many limitations of conventional obesity treatments.

Status of Obesity Management

Obesity is a chronic and complex disease, characterized by ectopic and excessive accumulation of adipose tissue (AT, commonly known as fat) that significantly increases the body weight and compromises the normal physiological function of AT [1]. Various therapeutic approaches for the treatment of obesity, such as lifestyle intervention, pharmacotherapy, and bariatric surgery, have been developed [2]. Lifestyle changes are the cornerstones of weight management, but they are difficult to achieve and to maintain. As a result, pharmacotherapy is typically considered an adjunctive treatment option [3].

Several antiobesity drugs and their therapeutic targets have been investigated in animals and humans. Six major therapeutic agents have been approved by the US FDA for obesity treatment: phentermine (Adipex-P®), orlistat (Xenical®), lorcaserin (Belviq®), liraglutide (Saxenda®), naltrexone/bupropion sustained release (Contrave®), and phentermine/topiramate extended release (Qsymia®). Most of these drugs work through central nervous system pathways to reduce appetite or enhance satiety, with the exception of orlistat, which decreases the absorption of fat [4]. However, inefficacy and risks of adverse effects have cast a long shadow over the development of many obesity therapeutic agents, leading to their withdrawn from the market [5]. Examples of adverse effects include pulmonary hypertension (aminorex), stroke (phenylpropanolamine), and neuropsychiatric issues (rimonabant) [6]. These undesirable experiences highlight the importance of risk–benefit assessments and necessitate the development of new drug delivery strategies to achieve safer and more efficient obesity treatment options.

Advanced drug delivery systems have been developed over recent decades using an array of materials and chemical strategies. Biocompatible polymers are particularly attractive drug carrier matrices due to the versatility in polymer chemistry and ease of tailoring their physicochemical and biological properties [7]. Polymeric carriers offer benefits in controlled and sustained delivery, extended drug bioactivity, and enhanced dissolution. Additionally, these carriers are gaining encouraging prospects in drug discovery because they could stabilize drugs and localize their effect to improve the therapeutic efficacy and specificity [8]. Several carriers have been designed to deliver antiobesity drugs to target different metabolic pathways (Figure 1). Compared with conventional pharmacotherapeutics, these new approaches have improved therapeutic efficiency and reduced adverse effects, and exhibit great potential for clinical translation. Here, we summarize some recent key developments in polymeric carriers for enhanced antiobesity drug delivery.

Conventional Treatments for Obesity and Their Limitations

Current treatments for obesity are generally prescribed based on the severity of excess weight and coexisting chronic conditions. Healthy lifestyle choices are considered the foundation of obesity

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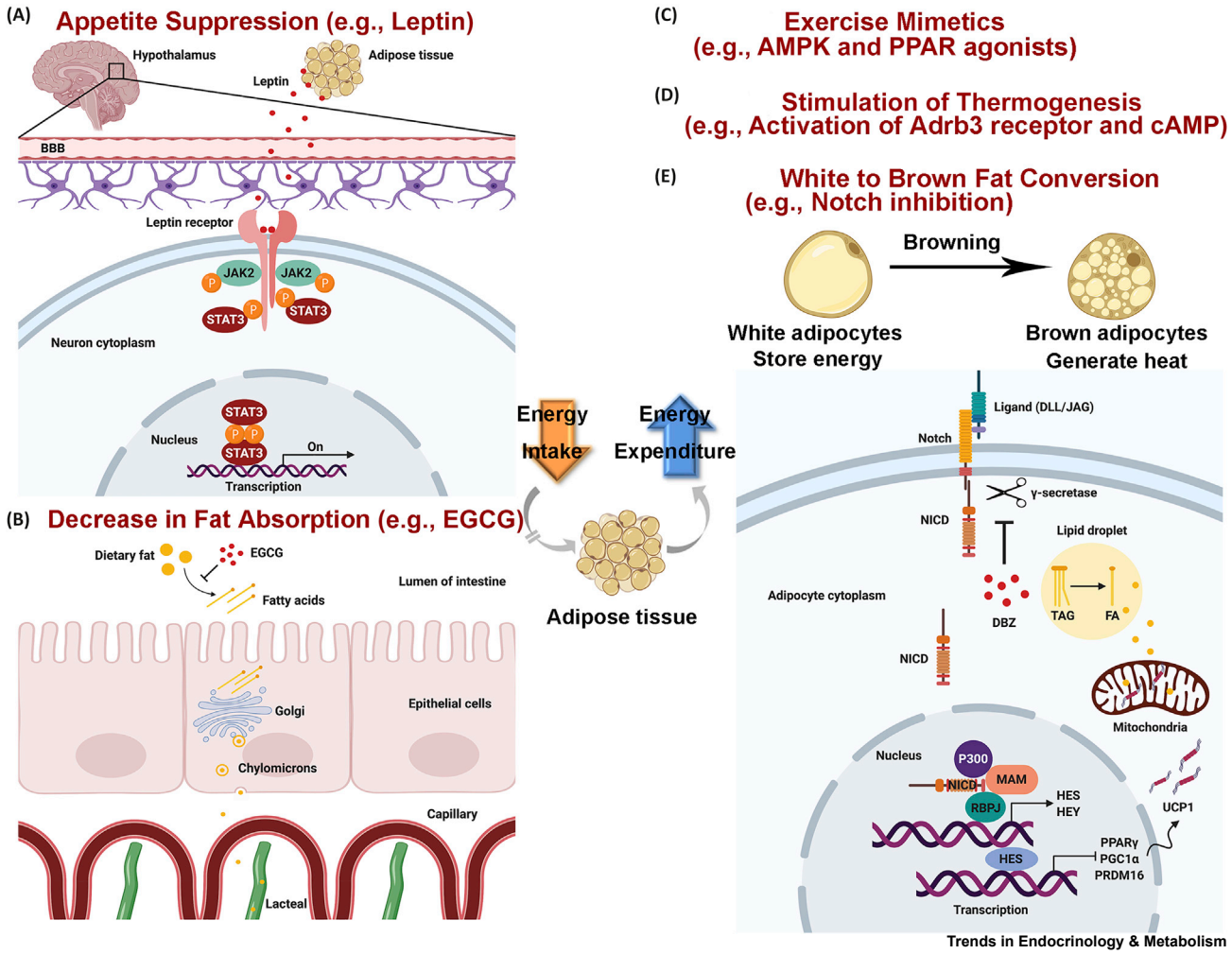

Figure 1. Key Antiobesity Strategies and Pharmacological Agents.

Reduced energy intake can be achieved through (A) appetite suppression: leptin secreted by adipocytes penetrates across the blood–brain barrier (BBB) and binds to neurons in the hypothalamus. Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling has been identified as a key pathway involved in activation of leptin receptors in the hypothalamus. Upon activation of the leptin pathway, synthesis of agouti-related neuropeptide and neuropeptide Y is inhibited, resulting in appetite suppression and decrease in food intake; and (B) decrease in fat absorption: large dietary fat breaks down and feeds a pool of dissolved monoglycerides and fatty acids. Once taken up by absorptive intestinal cells, they are packaged into chylomicrons and released into the lymphatic system. Epigallocatechin gallate (EGCG) has previously been shown to suppress fat absorption, with possible mechanisms including modified surface transport barriers and altered intraluminal digestion as well as intestinal production of lipoproteins. By contrast, strategies to increase energy expenditure include (C) exercise mimetics, such as 5′-AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPAR) agonists, which increase energy expenditure by muscle cells, which in turn release myokines to regulate adipose tissues; (D) stimulation of thermogenesis by brown adipocytes, which can be achieved through activation of β3-adrenal receptor (ADRB3), which relays sympathetic nerve signals to activate brown adipocytes, or activation of intracellular cAMP, a downstream mediator of ADRB3 signaling; and (E) white to brown fat conversion (termed 'browning'). For example, activation of Notch signaling leads to the release of Notch intracellular domain (NICD) via γ-secretase-mediated proteolytic cleavage. NICD translocates to the nucleus, where it binds the RBPJ transcriptional complex to activate the transcription of HES and HEY family genes. HES directly binds to the promoter regions of PR domain-containing 16 (PRDM16) and PPARγ coactivator 1α (PGC1α) to inhibit beige adipogenesis. Since the proteolytic cleavage of NICD is necessary for activation of Notch signaling, pharmacological blocking using a γ-secretase inhibitor dibenzazepine (DBZ) inhibits Notch signaling transduction and promotes browning of white adipocytes. Figure created using BioRender (https://biorender.com/). Abbreviations: DLL, delta like (Notch ligand); FA, fatty acids; JAG, jagged (Notch ligand); MAM, mastermind like transcriptional coactivator; TAG, triacylglyceride; UCP1, uncoupling protein 1.

Box 1. Commonly Used Bariatric Surgery Procedures

Bariatric surgery is an effective treatment for severe obesity and results in the improvement and remission of many obesity-related comorbidities and sustained weight loss [70]. The use of surgical procedures has dramatically escalated in recent years, with technical refinement of bariatric operations and initiation of an accreditation system to standardize surgery outcomes [71]. Currently, four types of bariatric surgery are commonly performed in the USA. Roux-en-Y gastric bypass was one of the first bariatric procedures developed and is still considered the gold-standard weight-loss operation [9]. This operation restricts food intake by creating a small pouch in the upper gastric fundus anastomosed to a Roux limb of jejunum and facilitating the consumption of less food and fewer calories [72]. Weight loss with Roux-en-Y gastric bypass is around 70% of excess weight at 1 year [73]. Laparoscopic adjustable gastric banding is the least invasive and safest procedure without inducing any anatomical gut changes. It involves an inflatable silicone band placed around the gastric fundus to create a small pouch and to result in a reduction in hunger [74]. Weight loss after laparoscopic adjustable gastric banding has been reported to be 34% of the excess weight at 1 year [75]. Laparoscopic sleeve gastrectomy, the most commonly used bariatric procedure in the USA, is constructed by removing 80% of the lateral aspect of the stomach in a vertical fashion and leaving a remaining long, tubular gastric pouch or sleeve. Weight loss from the sleeve gastrectomy has been reported to be 51–70% of excess weight at 1 year [75]. Lastly, biliopancreatic diversion with duodenal switch involves two distinct components. A vertical gastrectomy is first performed followed by bypassing a large portion of the small intestine to create malabsorption. Unlike the other procedures, a substantial amount of small bowel is bypassed with biliopancreatic diversion with duodenal switch, which results in a considerable decrease in the absorption of calories [76,77].

Although bariatric surgery yields short-term improvements in weight control, these procedures are generally associated with high costs, variations in outcomes, weight regain in 5–20% of patients, and risks of complications ranging from 10% to 17% [72,78]. Additionally, questions remain regarding their long-term safety, such as micronutrient deficiencies, the possibility of future abdominal procedures, potentially higher incidence of suicide, and excess skin that may require additional surgery for removal [79–82].

treatment, given their low costs and minimal risks. However, weight loss might lead to physiological adaptations that promote weight regain [2]. As a result, lifestyle modifications alone typically induce modest weight loss that is difficult to sustain. Therefore, additional treatment options for obesity have been used in the clinical setting, principally bariatric surgery (Box 1) and pharmacotherapy (Box 2) [3,9].

Advanced Drug Delivery Systems for the Treatment of Obesity

Despite great efforts made over the past decades, conventional therapeutic methods for obesity are often insufficient for preserving metabolic equilibrium and preventing life-threatening complications. Therefore, new strategies to improve their efficacy and to reduce adverse effects are critically needed for the management of obesity. Advances in biomaterials for drug delivery are enabling significant progress in medicine, with many polymeric carriers designed to release therapeutics for extended periods of time and further engineered to target specific locations or cell types within the body [10]. These polymeric carriers include polymer conjugates [11], hydrogels [12], microneedles [13], micro- and nanoparticles [14,15], and liposomes [16] (Figure 2). The utility of various drug delivery systems for obesity treatment are summarized in Table 1.

Polymer Conjugates

Polymer conjugates are commonly characterized by the presence of a rationally designed covalent bond between a polymer carrier and a bioactive drug molecule (Figure 2). These complexes release drugs as the polymers break down naturally over time or due to specific stimuli. The conjugated drug retains its bioactivity, but also acts as a building block in the assemblies. Polymer conjugates offer advantages over native therapeutics with functional modifications allowing tunable release and enhanced stability of native drugs.

Polymer conjugates capable of crossing biomembranes are a new strategy to improve delivery efficacy for appetite control and thermogenesis induction. Leptin is a regulatory protein secreted

Box 2. Current Pharmacotherapy Options

Pharmacotherapy is indicated as an adjunct to a reduced-calorie diet and increased activity for long-term weight management, bridging the gap between lifestyle modifications and invasive bariatric surgery [83]. Currently available medication on the market achieve their antiobesity effects via single or multiple mechanisms, principally including appetite suppression, decrease in fat absorption, and increase in energy expenditure [84]. Although efficacy has been found with monotherapies that target a single protein or pathway involved in obesity, with four monotherapy options (i.e., phentermine, orlistat, lorcaserin, and liraglutide) approved by the FDA, physiological counter-regulation mechanisms involving alternate pathways pose major limitations and lead to safety issues associated with cardiovascular and psychiatric complications [85]. Consequently, combined therapy is considered a more efficient way to treat a disease with multiple etiologies and two FDA-approved antiobesity combination products (i.e., phentermine/topiramate and naltrexone/bupropion) are currently on the market.

However, the magnitude of weight loss may be modestly effective and insufficient to eliminate the possibility for the development of comorbidities, necessitating the development of novel therapeutic candidates and targets. Most new drugs in the pipeline, including centrally acting agents and gut hormones as well as incretin targets, achieve their antiobesity effect via energy intake control [86]. Recently, a therapeutic strategy of boosting energy expenditure through stimulating thermogenesis has received more attention. Various factors have been identified to induce the transformation from white to beige adipose tissue (termed 'browning') and different browning agents, including a PPARγ activator, a β3-adrenoceptor agonist, and a Notch signaling inhibitor, have been investigated as potential antiobesity drugs [39,87,88].

Despite great efforts made to achieve therapeutic benefits, antiobesity drugs have considerable safety concerns that are attributed to the multifactorial pathogenesis and the complex neurohormonal regulation of energy balance, thereby influencing patient persistence and, in some cases, leading to withdrawal or restricted use of approved agents. For example, sibutramine, a combined serotonin and noradrenaline reuptake inhibitor, was withdrawn from the market in 2010 due to increased cardiovascular events in patients with pre-existing cardiovascular conditions [89]. Furthermore, numerous studies addressing the efficacy and safety of these pharmacological agents are still in their infancy and drugs currently under development appear unable to change this situation in the near future. As a result, a significant portion of obese patients have limited treatment options due to the minimal weight loss and adverse effects associated with current pharmacotherapies.

by adipocytes and acting within the brain to suppress appetite (Figure 1), but it generally shows resistance in the blood–brain barrier (BBB) due to impaired BBB transport and leptin receptor function in the hypothalamus that develop with obesity [17]. To overcome this challenge, leptin was conjugated with amphiphilic pluronic triblock copolymers [18]. Compared with unmodified leptin, leptin-pluronic P85 conjugates exhibited improved peripheral bioavailability and brain accumulation along with increased efficiency in reducing food intake in both ob/ob and high-fat diet (HFD)-induced obese mice. These results demonstrate that leptin analogs could be developed through chemical modification to facilitate penetration across the BBB, thus improving the efficacy for appetite control. To further optimize the chemical structure of conjugates, leptin was conjugated with pluronic P85 at various random lysine amino groups or specifically at its N-terminal amine [19]. Low-dose N-terminal conjugates with a reduced steric hindrance to leptin receptor binding were more efficiently transported to the brain and accumulated in the hypothalamus and hippocampus to a greater extent than the native leptin and random conjugates.

Obesity has been linked to chronic systemic inflammation initiated by proinflammatory macrophages in visceral AT [20]. However, conventional anti-inflammatory therapeutics at high doses may induce serious adverse effects in off-target tissues, particularly in hepatocytes, myocytes, and adipocytes. Therefore, specifically targeting visceral AT macrophages could substantially reduce toxicity. Dexamethasone, a corticoid with a half-life of 36–72 h, binds to the glucocorticoid receptor that inhibits the transcription of proinflammatory genes in M1 macrophages [21]. Dexamethasone-dextran conjugates were designed for selective uptake by macrophages due to their expression of dextran-binding C-type lectins and scavenger receptors [22]. Up to 63% of the injected conjugates remained in visceral AT 24 h after administration, especially those conjugated with high-molecular-weight dextran (70 and 500 kDa). The conjugated dexamethasone was slowly released after esterase hydrolysis and bound to

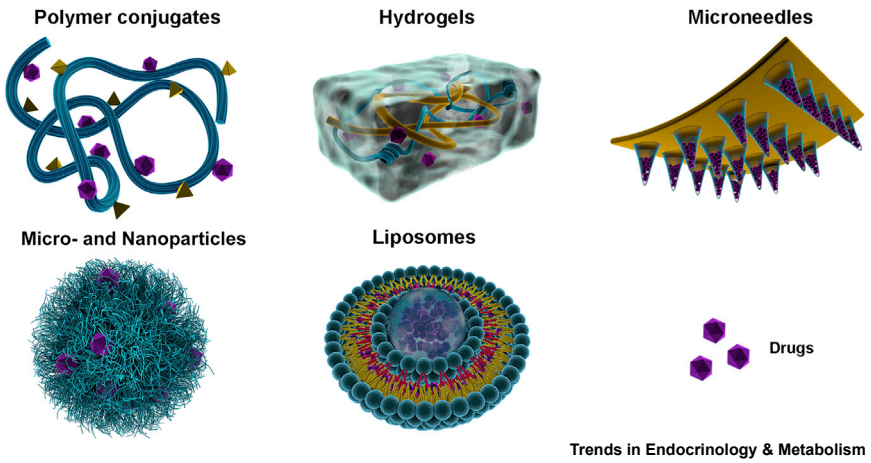

Figure 2. Advanced Drug Delivery Carriers for the Treatment of Obesity.
Drugs can be conjugated to the polymer chain (e.g., polymer conjugates), encapsulated into polymers (e.g., micro- and nanoparticles) or lipids (e.g., liposomes), or embedded within the carrier matrix (e.g., hydrogels and microneedles) to form the drug delivery system.

the glucocorticoid receptor that inhibits the transcription of proinflammatory genes in AT of obese mice.

Hydrogels

Hydrogels are 3D, crosslinked networks of water-soluble polymers (Figure 2). As drug carriers, hydrogels can provide spatiotemporal control over the release of therapeutics and leverage therapeutically beneficial outcomes of drug delivery. Owing to their tunable physicochemical properties, controllable degradability, and capability to protect drugs from degradation, hydrogels serve as a platform on which various physiochemical interactions with the biomolecules occur to control drug release and enhance therapeutic efficacy [23].

Epigallocatechin gallate (EGCG), the most abundant catechin in green tea, with half-lives ranging from 1.9 to 4.6 h, has shown great potential as an antiobesity treatment via decreasing fat absorption (Figure 1) [24,25]. However, its poor bioavailability limits its clinical application. Zhang *et al.* developed EGCG-loaded *in situ* hydrogel implants using poly(lactic-co-glycolic acid) (PLGA) and administered the implants to HFD-induced obese mice [26]. Over a 30-day period, the hydrogel-EGCG implant group showed a 35.6% reduction in body-weight gain compared with the control group. Also, the hydrogel-EGCG implant treated mice had lower levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride, and higher levels of high-density lipoprotein (HDL) cholesterol. These findings suggest that *in situ* hydrogel implants are a promising drug delivery system for prolonged antihyperlipidemic and antiobesity treatment.

Hybrid hydrogels can also be fabricated to offer opportunities for controlled drug release. Liao *et al.* loaded leptin in methylcellulose-based hydrogels with incorporation of gold nanoparticles [27]. The temperature-dependent degradation of hydrogels was controlled by the proportion of gold nanoparticles. Leptin released from hydrogels accumulated in AT, inhibiting fat storage in adipocytes following a tunable light irradiation response. Considering the encouraging *in vitro* results, further studies on the *in vivo* feasibility of this stimuli-responsive hydrogel system are warranted.

Microneedles

As a drug delivery system, microneedles provide an alternative administration method through surface skins and have been used in the clinic [28]. A microneedle patch usually comprises arrays of microscopic needles typically with a height of 500–800 μm that can overcome the transport barrier

Table 1. Summary of Advanced Material Carriers Applied in the Treatment of Obesity[a]

Advantages	Disadvantages	Applications in the treatment of obesity					
		Administration route	Carrier matrix	Modification	Therapeutic agents	Experimental model	Refs
Chemical conjugates							
Drug release in controlled and sustained manner; improvement in aqueous solubility of drug and its bioavailability; prolong blood plasma half-life of drug	Low drug loading; Large sized conjugates have potential for long-term accumulation, resulting in toxicity; conjugates are taken up slowly by endocytosis	N.A.	Low-molecular-weight protamine	N.A.	ASO for HIF1α	3T3-L1 cell line	[60]
		Intraperitoneal injection	Low-molecular-weight protamine	N.A.	ASO for HIF1α	Lean or HFD-induced obese mice	[11]
		Local injection	D-form 9-arginine	Adipose-homing peptide (CKGGRAKDC)	shRNA silencing FABP-4	HFD-induced obese mice	[61]
		Intravenous injection	Dextran	PEG	Dexamethasone	Lean or HFD-induced obese mice	[22]
		Intracerebroventricular, intravenous, or subcutaneous injection	Pluronic P85	N.A.	Leptin	Ob/ob mice or HFD-induced obese mice	[18]
		Intracerebroventricular or intranasal injection	Pluronic P85	N-terminal group	Leptin	Lean mice	[19]
Hydrogels							
Drug release in controlled and sustained manner; good diffusional properties; biocompatibility and biodegradability; *in situ* gelling systems at body temperature can be made	Low mechanical resistance; difficult to control pore size and degradation rate; potential toxicity posed by chemical crosslinkers	Subcutaneous injection	PLGA	N.A.	EGCG	Mice fed HFD or normal diet	[26]
		N.A.	Methylcellulose-gold nanoparticles	N.A.	Leptin	3T3-L1 cells	[27]

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Table 1. *Continued*

Advantages	Disadvantages	Applications in the treatment of obesity					
		Administration route	Carrier matrix	Modification	Therapeutic agents	Experimental model	Refs
Microneedles							
Non-invasive administration; ease of administration; specific tissue area can be targeted for desired drug delivery with minimized systemic adverse effects	Difficult insertion into target tissue by hand without external device; local inflammation may be induced if amount of drug is high; limited choice of appropriate biomaterials and lack of mechanical strength	Intradermal insertion	HA and PLGA	N.A.	CL316243 or T3	HFD-induced obese mice	[30]
		Intradermal insertion	HA	N.A.	Caffeine	HFD-induced obese mice	[31]
		Intradermal insertion	Gelatin	N.A.	Glycerol	HFD-induced obese rats	[32]
		Intradermal insertion	Methacrylated HA-dextran nanoparticles	Glucose oxidase and catalase	Rosiglitazone or CL316243	Lean or HFD-induced obese mice	[13]
Microparticles							
Drug release in controlled and sustained manner; protection of drugs against the environment; aid dispersal of water-insoluble drugs in aqueous media; localize at application site	Limited ability to cross biological barriers and enter cells due to relatively large particle size; inflammatory response might be elicited due to slow degradation of particulate materials	Oral administration	PCL	N.A.	Capsaicinoids	Obese rats induced by hypothalamic lesion using monosodium L-glutamate	[36]
		Oral administration	Chitosan	N.A.	Capsaicinoids	HFD-induced obese rats	[37]
		Oral administration	Chitosan or water-soluble chitosan	N.A.	N.A.	Rats fed HFD or normal diet	[62]
		Local injection	PLGA	N.A.	DBZ	Lean mice	[14]
		Bilateral injection into paraventricular hypothalamic nucleus	Human serum albumin-alginate	N.A.	α-MSH	Lean rats	[38]

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Table 1. *Continued*

Advantages	Disadvantages	Applications in the treatment of obesity					
		Administration route	Carrier matrix	Modification	Therapeutic agents	Experimental model	Refs
Nanoparticles							
Drug release in controlled and sustained manner; tunable physicochemical properties; easy to functionalize; excellent ability to penetrate across biological barriers	Difficulty for scale-up; Insufficient of toxicity assessment in literature	Oral administration	Chitosan or water-soluble chitosan	N.A.	N.A.	Rats fed HFD or normal diet	[62]
		Intraperitoneal injection	Cerium oxide	N.A.	N.A.	Lean rats	[63]
		Local injection	PLGA	N.A.	DBZ	HFD-induced obese mice	[49]
		N.A.	PLGA-*b*-PEG	TPP	2,4-DNP	3T3-L1 cell line	[48]
		Intravenous injection	PLGA-*b*-PEG	iRGD or P3	Rosiglitazone or prostaglandin E2 analog	Lean or HFD-induced obese mice	[47]
		Intravenous injection	Gold	Biotinylated adipose-homing peptide (CKGGRAKDC) and PEG	N.A.	Mice fed HFD or normal diet	[64]
		Retro-orbital injection	PLGA	N.A.	Rosiglitazone	*Ldlr*$^{-/-}$ mice fed HFD	[44]
		Intravascular injection	*Bifidobacterium* shuttle vector	N.A.	OXM	Normal or overweight mice	[65]
		Intravenous injection	Cadmium-based quantum dots	Adipose-homing peptide (CKGGRAKDC)	N.A.	Rats fed HFD or normal diet	[66]
		Retro-orbital injection	PCL or mesoporous silica	N.A.	N.A.	Lean or HFD-induced obese mice	[59]

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Table 1. *Continued*

Advantages	Disadvantages	Applications in the treatment of obesity					
		Administration route	Carrier matrix	Modification	Therapeutic agents	Experimental model	Refs
Liposomes							
Drug release in controlled and sustained manner; biocompatibility and biodegradability; low toxicity and antigenicity	Low stability; phospholipids may undergo oxidation and hydrolysis; leakage of encapsulated drugs during storage	Oral administration	Linseed oil	N.A.	Capsaicin and phenylalaninol oleamide or oleoylethanolamide	HFD-induced obese mice	[67]
		N.A.	Soy L-α-phosphatidylcholine	N.A.	Resveratrol	3T3-L1 cell line	[16]
		Intraperitoneal injection	DSPC and CDAN	PEG	Acetate	Lean or HFD-induced obese mice	[68]
		N.A.	Egg yolk phosphatidylcholine	Adipose tissue-specific circular peptide (KGGRAKD)	N.A.	Primary endothelial cells derived from white adipose tissue	[52]
		Intravenous injection	Egg yolk phosphatidylcholine	Adipose tissue-specific circular peptide (KGGRAKD)	N.A.	Lean or HFD-induced obese mice	[53]
					$_{D}$(KLAKLAK)$_2$	Lean or HFD-induced obese mice	[54]
					Cytochrome C	Mice fed with HFD or normal diet	[55]
			Lipid-latex	Phosphatidylserine and cholesterol-9-carboxynonanoate	Rosiglitazone, paclitaxel, and tamoxifen	FmsYFP$^+$ mice fed HFD or normal diet; *ApoE*$^{-/-}$ or wild-type mice	[69]

[a]Abbreviations: CDAN, *N*[1]-cholesteryloxycarbonyl-3,7-diazanonane-1,9-diamine; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; N.A., not available.

posed by epidermis and directly localize therapeutic agents in a minimally invasive manner (Figure 2). These needles can be made of water-soluble or biodegradable polymers encapsulating drug that is released in the insertion site upon microneedle dissolution or degradation. The local diffusion and accumulation of transdermally delivered drugs allow targeted delivery into subcutaneous AT and minimize systemic adverse effects [29].

Than *et al*. developed microneedle patches using hyaluronic acid (HA) and PLGA to deliver an anti-obesity compound to the subcutaneous white AT [30]. Specifically, the β3-adrenoceptor agonist CL316243, widely used to convert white fat to brown fat (browning, Figure 1), was released from microneedles. The released drugs reached inguinal AT underneath the insertion sites, promoted browning of white AT, and suppressed body fat as well as weight gain in HFD-induced obese mice. Also, the microneedle delivery requires a lower effective dosage compared with systemic administration, thus minimizing potential adverse effects of overactivating β3-adrenoceptors. HA-based microneedles were also used to deliver caffeine, shown to be able to reduce body weight through stimulating lipolysis but exhibiting low bioavailability due to its polymorphic transformation from an anhydrous to hydrous form [31]. Loading caffeine into dissolvable HA microneedles inhibited its crystal growth and significantly improved lipolysis, which reduced the levels of triglyceride, total cholesterol, and LDL cholesterol, leading to a weight loss of 12.8% in HFD-induced obese mice. More recently, microneedle-mediated delivery of natural polymers for obesity treatment was reported by An *et al*. [32]. Their results showed that gelatin microneedles alone, without entrapping any therapeutics, reduced the amount of subcutaneous AT by ~60%, through inducing lipolysis and inhibiting lipogenesis in an HFD-induced obese rat model. This effect might be mediated by glycine, which constitutes 30% of amino acids in gelatin and has previously been shown to reduce body weight and adipose tissue [33]. The potential of drug-loaded gelatin formulations for obesity treatment is enormous considering these current results; however, their safety (immunogenicity) profile and pharmacological mechanisms should be carefully evaluated in the future.

Microneedles can also be an effective vehicle for the intradermal delivery of nanoparticles, where the microconduits in the epidermis produced by microneedles serve as channels for nanoparticles to enter the therapeutic sites. Zhang *et al*. developed a transcutaneous patch based on polymeric microneedles to locally deliver antiobesity therapeutics and induce AT transdifferentiation [13]. These authors used pH-sensitive acetal-modified dextran nanoparticles to encapsulate browning agents CL 316243 or rosiglitazone for sustained release. These drug-loaded particles were further embedded into the crosslinked HA-based microneedle array to penetrate the skin and restrict the agents to the inguinal AT. Under physiological glucose conditions, pH-sensitive nanoparticles gradually degraded to release the agent into the AT and to promote browning. The *in vivo* results on HFD-induced obese mice indicated that this microneedle formation increased systemic energy expenditure and fatty acid oxidation, improved insulin sensitivity, and inhibited weight gain (~15%).

Microparticles

Particulate drug delivery overcomes the limitation of microneedles, which are typically used for local drug delivery. Particles share similar advantages with hydrogel implants and microneedles in terms of the direct deposition at the therapeutic site with a high local drug concentration and minimized systemic toxicity (Table 1). They can also be used as reservoirs, administered through a convenient route with the drug slowly released for systematic effect. Additionally, particles can be administered systemically but delivered to specific locations to release the encapsulated drugs through active or passive targeting approaches [34]. A distinction is often made between microparticles and nanoparticles, with particles with dimensions best described in the micrometer and nanometer ranges, respectively (Figure 2). The difference in particle size translates into differences in many aspects, from *in vitro* characteristics to *in vivo* usage.

Consumption of capsaicinoids increase energy expenditure by 50 kcal/day, which produces a clinically significant weight loss within 1–2 years [35]. However, their pungency limits their long-term use through the gastrointestinal tract. Almeida *et al*. encapsulated capsaicin into polycaprolactone

(PCL) microparticles [36]. Capsaicin was slowly released from PCL microparticles in a controlled manner without changing its biexponential release kinetic. The optimized particulate formulation efficiently enhanced the gastric tolerability of capsaicin by preventing inflammation in the submucosal layer of stomach and decreased mesenteric and retroperitoneal fat deposits in obese rats. Capsaicin-encapsulated chitosan microspheres have also been developed and their antiobesity effects following oral administration were evaluated in HFD-induced obese rats [37]. Compared with native capsaicin and the commercial agent orlistat, capsaicin-encapsulated microspheres exhibited an enhanced ability to control body weight, body fat, and serum lipids.

Local injection into the target tissue is a promising approach to achieve site specificity. Microparticles have also been administered via local injections for obesity treatment due to their favorable characteristics to avoid rapid diffusion of drugs and prolong their local retention. Lucas *et al.* prepared human serum albumin-alginate microparticles encapsulating α-melanocyte-stimulating hormone (α-MSH), an anorexigenic neuropeptide that has antiobesity effects [38]. Microparticles administered via hypothalamic injections were able to slowly release α-MSH in the hypothalamus to specifically target paraventricular nucleus and protected the peptide from degradation. Compared with blank particles and native α-MSH groups, rats receiving α-MSH-loaded particles showed a sustained decrease in body weight gain.

PLGA microparticles have also been used to locally inhibit Notch signaling in AT [14]. Notch signaling promotes adipocyte browning and improves energy metabolism (Figure 1) [39,40]. Dibenzazepine (DBZ) is a well-established inhibitor of Notch signaling, but systemic inhibition of Notch may exhibit off-target toxicity in the gastrointestinal tract [41]. DBZ-loaded PLGA microparticles were prepared and their effects on locally induced browning of white AT were investigated in lean mice. Results show that DBZ released from microparticles following local injections into the inguinal white AT retained its bioactivity and efficiently promoted browning of white adipocytes through inhibition of Notch signaling. More importantly, the localized release of DBZ in the inguinal white AT overcame the potential adverse effects induced by systemic administration. Although microparticles show potential for controlled drug delivery by providing a high local drug concentration over an extended period, challenges remain to be addressed in their application (Table 1). For instance, microparticles are unlikely to cross most biological barriers due to their large size. Also, they can elicit acute and chronic inflammatory response resulting from slow degradation of particulate materials.

Nanoparticles

Nanoparticles overcome some of the limitations faced by microparticles (Table 1). They are characterized by several additional benefits, such as a large surface:volume ratio, intracellular drug release, and tunable surface chemistry, making them promising delivery systems for disease treatments, including obesity [42]. Their geometrical and physicochemical properties can be finely tuned during their synthesis to optimize drug loading and enhance specificity in reaching the target cells and/or tissues, thereby increasing the therapeutic efficacy and minimizing adverse effects [43].

Systemic administration is a powerful delivery route for obesity treatment. Di Mascolo *et al.* fabricated rosiglitazone-encapsulated PLGA nanoparticles, surrounded by an outer layer of steric repulsive polyvinyl alcohol (PVA) to reduce the aggregation of nanoparticles and attenuate protein modification and opsonization in the blood after intravascular injection [44]. HFD-fed $Ldlr^{-/-}$ mice treated with nanoparticles showed alleviation of inflammatory macrophages in the white AT and liver, without adverse effects on lipid metabolism and cardiac tissues, which are typically observed following systemic administration of native rosiglitazone.

Efficient drug delivery to specific therapeutic targets is always challenging. Nanoparticles can be modified with surface ligands, targeting molecules, or peptides for efficient navigation to the therapeutic sites. Given that angiogenic factors crosstalk among cells in AT and stimulation of angiogenesis results in browning of AT [45,46], vasculature-directed targeting of AT could be a potential therapeutic intervention for obesity. Xue *et al.* used PLGA-*b*-poly(ethylene glycol) (PEG)

nanoparticles to encapsulate rosiglitazone or a prostaglandin E2 analog, and modified the nanoparticle surface with adipose vasculature-targeted peptides iRGD (CRGDK/RGPD/EC) or P3 (CKGGRAKDC), which bind to antigens specifically expressed on the endothelium of angiogenic vasculature [47]. As a result, more targeted nanoparticles localized in the AT to release drugs following intravenous injection compared with free drugs and nontargeted nanoparticles. This approach enhanced browning of white AT and inhibited body-weight gain in HFD-induced obese mice.

AT mitochondrial dysfunction is generally linked to obesity, but to efficiently deliver drugs to the mitochondria is one of the most challenging tasks. Marrache and Dhar developed mitochondria-targeting polymeric nanoparticles by blending a targeted PLGA-*b*-PEG-triphenylphosphonium (TPP) polymer with either nontargeted PLGA-*b*-PEG-OH or PLGA-COOH [48]. Targeted nanoparticles achieved high endolysosomal escapability and mitochondrial uptake efficacy due to their high buffering capacity. In addition, the efficacy could be adjusted by fine-tuning the surface charge and size of the nanoparticles. Moreover, targeted nanoparticles encapsulating mitochondrial uncoupler 2,4-DNP suppressed differentiation of 3T3-L1 preadipocytes at a lower dose compared with the free drug.

Local drug delivery for the treatment of obesity has recently been investigated due to its ability to maintain drug bioavailability and permit a reduction in dosage. Jiang *et al*. encapsulated DBZ into PLGA nanoparticles and locally injected them into inguinal white AT in HFD-induced obese mice to stimulate browning of white adipocytes, improve the glucose homeostasis, and attenuate body-weight gain through inhibition of the Notch signaling pathway [49]. Notably, nanoparticles were preferentially endocytosed by adipocytes following local administration, limiting the therapeutic agent to be distributed throughout the body and reducing the adverse effects on no-adipocyte cells. DBZ-loaded nanoparticles also efficiently inhibited Notch signaling with a dosage 50 times lower than that through intraperitoneal injection and ten times lower than that using microparticles due to enhanced intracellular delivery.

Liposomes

Liposomes, sphere-shaped vesicles comprising one or more concentric lipid bilayers, represent another carrier for drug delivery (Figure 2) [50]. These carriers tend to interact or fuse with cells indiscriminately during systemic circulation and can be used as contact-facilitated delivery through lipid–lipid exchange between cell membrane and the lipid layer of liposomes [51]. The nonspecific cellular uptake and uncontrolled entrapment in nontargeted organs are undesired for liposomal drug delivery via systemic administration, but can be overcome by modifying a hydrophilic polymer, such as PEG, onto the surface of liposomes, which enables minimal uptake by the reticuloendothelial system, reduced renal clearance, and prolonged retention in circulation [43]. Therefore, the therapeutic agent is better able to be retained in the body to exert its therapeutic potency.

To achieve enhanced drug delivery efficacy to AT, a variety of ligand-based functionalized liposomes have been developed and appear to be superior in specificity and safety. Hossen *et al*. modified the surface of liposomes with PEG and a circular peptide (KGGRAKD), which specifically binds to endothelial cell-surface prohibitin in white adipose vessels [52,53]. The liposomes were specifically taken up by primary endothelial cells isolated from inguinal white AT via prohibitin-mediated endocytosis and escaped from endosomes and lysosomes. Compared with nonPEGylated targeted liposomes, PEGylated targeted liposomes achieved enhanced accumulation in white adipose vessels of lean mice following intravenous administration, whereas undesired particle accumulation in the liver was considerably reduced. Moreover, targeted liposomes exclusively accumulated in both adipose vessels and angiogenic clusters of adipocytes after systemic administration in obese mice. Surprisingly, PEGylated nontargeted liposomes were also observed in these clusters via an unexpected passive targeting mechanism, potentially due to enhanced tissue permeability and retention effect. In following studies, antiobesity therapeutics, such as proapoptotic peptide $_{D}(KLAKLAK)_{2}$ and apoptosis-initiating protein cytochrome C, were encapsulated in the prohibitin-targeted

nanoparticles [54,55]. Systemic administration of targeted nanoparticles in HFD-induced obese mice substantially reduced body-weight gain, serum leptin levels, and ectopic fat deposits in the liver and muscle. Additionally, no detectable hepatotoxicity associated with this prevention was observed, suggesting that this targeted liposomal formulation had good biocompatibility and safety.

Challenges and Future Opportunities of Advanced Drug Delivery Strategies

Given the aforementioned advances, controlled drug delivery strategies could revolutionize the treatment of obesity. However, there is an urgent need to fully understand the advantages and disadvantages of these formulations (Table 1) and to overcome challenges for clinical translation. It will be key to discover the fate of carriers following administration and mechanisms underlying their toxicity, and how to achieve high reproducibility and scale-up in industry.

The primary aim of preclinical evaluation is to identify the therapeutic potential and risks, to select formulations that are safe and efficacious, and that have the required pharmacokinetic and biodistribution properties. Since the off-target toxicities of delivery systems may be different from the parent drug, it is important to accurately assess their biodistribution within the body after administration and their interaction with targeted cells before use. Obesity is often associated with chronic inflammation, reduced blood flow to the AT, increased glomerular filtration, and histological alterations of the liver. As a result, obesity could interfere carrier biodistribution, degradation, and loading dose parameters [56]. However, there are few studies investigating the fate of delivery systems in obesity, with the factors dictating carrier interactions within living systems largely ignored. It is commonly believed that nanoparticles with a particle size of 15–200 nm are typically captured by the liver Kupffer cells, whereas those > 200 nm are retained in the spleen after administration [57,58]. However, de Jesus Felismino *et al.* recently found an opposite trend in obese subjects [59]. Large nanoparticles (280 nm) were principally taken up by Kupffer cells, while small nanoparticles (58 nm) preferentially deposited in the spleen. Their results also suggested that the particle size of carriers has a predominant effect on biodistribution, especially regarding deposition in spleen, which tends to be more permeable to small particles under pathological conditions associated with obesity. In addition to the characteristics of drug carriers, fat depots and administration routes also affect their biodistribution [22]. For instance, the portal-drained visceral fat depots are more lipolytically active and more permeable to particles compared with the subcutaneous fat pads, particularly in obese patients. Also, drug carriers administered via the intraperitoneal route can be directly deposited in the targeted AT through a positive hydrostatic pressure generated by injected liquids, which allows rapid physical access of the drug to the adipose interstitium. Further studies are required to understand the fate of both the carrier and drug following application before translating these formulations into the clinic.

Despite growing attention to the advantages of novel drug carriers for obesity treatment, further studies are needed to assess whether the benefits outweigh the risks. Also, the antiobesity efficacy of these carriers has often not been investigated in larger mammals; therefore, the feasibility of their use is less clear compared with the therapeutics themselves. The safety of drug carriers should be particularly considered, since formulations applied at a wrong dose or in a susceptible patient may give rise to unexpected toxicity. Luckily, recent research efforts have been made towards establishing standardized *in vitro* assays for the biocompatibility evaluation of carrier materials and *ex vivo* models for predicting the biological and toxicological responses of drug carriers through specific routes of administration [57].

Another challenge that requires consideration is detailed characterization of the physicochemical properties of these delivery systems. Compared with native drugs, it is more complex to thoroughly characterize drug-encapsulated carriers. These systems might be intrinsically heterogeneous resulting from polydispersity and batch-to-batch variations. Also, the degradation rate and mechanism of biodegradable polymers are other complicating factors in many cases, particularly for hybrid materials. Despite the complexity in experimental designs, systematic physicochemical characterizations of these formulations could contribute to the understanding of their biological and toxicological responses, development of subsequent generations for enhanced therapeutic efficacy, and transfer of formulations into the clinic.

Concluding Remarks

Pharmacotherapy has an important role in the management of obesity, but the therapeutic efficacy of conventional medication is limited with adverse effects. A variety of novel drug delivery strategies for obesity treatment have been developed to provide a targeted or intelligent platform to release therapeutics in a spatiotemporally controlled manner, thereby achieving enhanced antiobesity efficacy and reduced toxicity. Although clinical translation of these formulations remains challenging and further explorations that take industrial and clinical perspectives into account are warranted (see Outstanding Questions), there are already successful preclinical studies involving these delivery strategies, which could have a significant impact on bringing safe and effective therapies to obese patients in the future.

Outstanding Questions

Are the benefits of polymeric carriers shown in small animals applicable to large mammals?

Can standardized *in vitro* and *ex vivo* assays for the safety evaluation of carriers be performed to accurately predict their biological and toxicological properties?

Can the encapsulation of antiobesity agents into polymeric carriers achieve controlled pharmacokinetics and target specificity required for efficacious obesity treatment in humans?

Will safety issues arise from the use of polymeric carriers or degraded materials in humans?

Will polymeric carriers for the treatment of obesity in clinical trials result in beneficial long-term outcomes?

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References

1. Pilitsi, E. *et al.* (2018) Pharmacotherapy of obesity: available medications and drugs under investigation. *Metabolism* 92, 170–192
2. Heymsfield, S.B. and Wadden, T.A. (2017) Mechanisms, pathophysiology, and management of obesity. *N. Engl. J. Med.* 376, 254–266
3. Apovian, C.M. *et al.* (2015) Pharmacological management of obesity: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 100, 342–362
4. Srivastava, G. and Apovian, C.M. (2018) Current pharmacotherapy for obesity. *Nat. Rev. Endocrinol.* 14, 12–24
5. Kang, J.G. and Park, C.Y. (2012) Anti-obesity drugs: a review about their effects and safety. *Diabetes Metab. J.* 36, 13–25
6. Krentz, A.J. *et al.* (2016) Evolution of pharmacological obesity treatments: focus on adverse side-effect profiles. *Diabetes, Obes. Metab.* 18, 558–570
7. Kumbar, S.G. *et al.* eds (2014). Natural and Synthetic Biomedical Polymers Newnes
8. Tibbitt, M.W. *et al.* (2016) Emerging frontiers in drug delivery. *J. Am. Chem. Soc.* 138, 704–717
9. Iovino, P. *et al.* (2015) Bariatric surgery worldwide 2013. *Obes. Surg.* 25, 1822–1832
10. Fenton, O.S. *et al.* (2018) Advances in biomaterials for drug delivery. *Adv. Mater.* 30, 1705328
11. Park, Y.S. *et al.* (2012) In vivo delivery of cell-permeable antisense hypoxia-inducible factor 1α oligonucleotide to adipose tissue reduces adiposity in obese mice. *J. Control. Release* 161, 1–9
12. Qi, D. *et al.* (2018) Effects of tunable, 3D-bioprinted hydrogels on human brown adipocyte behavior and metabolic function. *Acta Biomater* 71, 486–495
13. Zhang, Y. *et al.* (2017) Locally induced adipose tissue browning by microneedle patch for obesity treatment. *ACS Nano* 11, 9223–9230
14. Jiang, C. *et al.* (2015) Biodegradable polymeric microsphere-based drug delivery for inductive browning of fat. *Front. Endocrinol. (Lausanne).* 6, 1–11
15. Lee, S. *et al.* (2019) Intravenous sustained-release nifedipine ameliorates nonalcoholic fatty liver disease by restoring autophagic clearance. *Biomaterials* 197, 1–11
16. Zu, Y. *et al.* (2018) Resveratrol liposomes and lipid nanocarriers: comparison of characteristics and inducing browning of white adipocytes. *Colloids Surf. B Biointerfaces* 164, 414–423
17. Myers, M.G., Jr. *et al.* (2010) Obesity and leptin resistance: distinguishing cause from effect. *Trends Endocrinol. Metab.* 21, 643–651
18. Yi, X. *et al.* (2014) Pluronic modified leptin with increased systemic circulation, brain uptake and efficacy for treatment of obesity. *J. Control. Release* 191, 34–46
19. Yuan, D. *et al.* (2017) Intranasal delivery of N-terminal modified leptin-pluronic conjugate for treatment of obesity. *J. Control. Release* 263, 172–184
20. Saltiel, A.R. and Olefsky, J.M. (2017) Inflammatory mechanisms linking obesity and metabolic disease. *J. Clin. Invest.* 127, 1–4
21. Graversen, J.H. *et al.* (2012) Targeting the hemoglobin scavenger receptor CD163 in macrophages highly increases the anti-inflammatory potency of dexamethasone. *Mol. Ther.* 20, 1550–1558
22. Ma, L. *et al.* (2016) Efficient targeting of adipose tissue macrophages in obesity with polysaccharide nanocarriers. *ACS Nano* 10, 6952–6962
23. Li, J. and Mooney, D.J. (2016) Designing hydrogels for controlled drug delivery. *Nat. Rev. Mater.* 1, 16071
24. Klaus, S. *et al.* (2005) Epigallocatechin gallate attenuates diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation. *Int. J. Obes.* 29, 615–623
25. Li, F. *et al.* (2018) EGCG reduces obesity and white adipose tissue gaining partly through AMPK activation in mice. *Front. Pharmacol.* 9, 1366

26. Zhang, X.-Z. *et al.* (2015) Polymeric in situ hydrogel implant of epigallocatechin gallate (EGCG) for prolonged and improved antihyperlipidemic and anti-obesity activity: preparation and characterization. *J. Biomater. Tissue Eng.* 5, 813–817
27. Liao, Z.X. *et al.* (2017) Light-triggered methylcellulose gold nanoparticle hydrogels for leptin release to inhibit fat stores in adipocytes. *Int. J. Nanomedicine* 12, 7603–7611
28. Prausnitz, M.R. (2017) Engineering microneedle patches for vaccination and drug delivery to skin. *Annu. Rev. Chem. Biomol. Eng.* 8, 177–200
29. Zhang, Y. *et al.* (2018) The potential of a microneedle patch for reducing obesity. *Expert Opin. Drug Deliv.* 15, 431–433
30. Than, A. *et al.* (2017) Transdermal delivery of anti-obesity compounds to subcutaneous adipose tissue with polymeric microneedle patches. *Small Methods* 1, 1700269
31. Jung, H. *et al.* (2017) Anti-obesity effect of a novel caffeine-loaded dissolving microneedle patch in high-fat diet-induced obese C57BL/6J mice. *J. Control. Release* 265, 41–47
32. An, S.M. *et al.* (2018) Intracutaneous delivery of gelatins induces lipolysis and suppresses lipogenesis of adipocytes. *Acta Biomater* 67, 238–247
33. Reyes Lopez, Y. *et al.* (2016) Effect of glycine on adipocyte hypertrophy in a metabolic syndrome rat model. *Curr. Drug Deliv.* 13, 158–169
34. Kohane, D.S. (2007) Microparticles and nanoparticles for drug delivery. *Biotechnol. Bioeng.* 96, 203–209
35. Whiting, S. *et al.* (2012) Capsaicinoids and capsinoids. A potential role for weight management? A systematic review of the evidence. *Appetite* 59, 341–348
36. Almeida, M.A. *et al.* (2014) Enhanced gastric tolerability and improved anti-obesity effect of capsaicinoids-loaded PCL microparticles. *Mater. Sci. Eng. C* 40, 345–356
37. Tan, S. *et al.* (2014) Antiobese effects of capsaicin-chitosan microsphere (CCMS) in obese rats induced by high fat diet. *J. Agric. Food Chem.* 62, 1866–1874
38. Lucas, N. *et al.* (2015) Chronic delivery of α-melanocyte-stimulating hormone in rat hypothalamus using albumin-alginate microparticles: effects on food intake and body weight. *Neuroscience* 290, 445–453
39. Bi, P. *et al.* (2014) Inhibition of Notch signaling promotes browning of white adipose tissue and ameliorates obesity. *Nat. Med.* 20, 911–918
40. Bi, P. and Kuang, S. (2015) Notch signaling as a novel regulator of metabolism. *Trends Endocrinol. Metab.* 26, 248–255
41. Barten, D.M. *et al.* (2006) γ-Secretase inhibitors for Alzheimer's disease. *Drugs R. D.* 7, 87–97
42. Tsou, Y.H. *et al.* (2019) Nanotechnology-mediated drug delivery for the treatment of obesity and its related comorbidities. *Adv. Healthc. Mater.* 8, e1801184
43. Ash, G.I. *et al.* (2019) Promises of nanotherapeutics in obesity. *Trends Endocrinol. Metab.* 30, 369–383
44. Di Mascolo, D. *et al.* (2013) Rosiglitazone-loaded nanospheres for modulating macrophage-specific inflammation in obesity. *J. Control. Release* 170, 460–468
45. Cao, Y. (2007) Angiogenesis modulates adipogenesis and obesity. *J. Clin. Invest.* 117, 2362–2368
46. Cao, Y. (2010) Adipose tissue angiogenesis as a therapeutic target for obesity and metabolic diseases. *Nat. Rev. Drug Discov.* 9, 107–115
47. Xue, Y. *et al.* (2016) Preventing diet-induced obesity in mice by adipose tissue transformation and angiogenesis using targeted nanoparticles. *Proc. Natl. Acad. Sci.* 113, 5552–5557
48. Marrache, S. and Dhar, S. (2012) Engineering of blended nanoparticle platform for delivery of mitochondria-acting therapeutics. *Proc. Natl. Acad. Sci.* 109, 16288–16293
49. Jiang, C. *et al.* (2017) Dibenzazepine-loaded nanoparticles induce local browning of white adipose tissue to counteract obesity. *Mol. Ther.* 25, 1718–1729
50. Sercombe, L. *et al.* (2015) Advances and challenges of liposome assisted drug delivery. *Front. Pharmacol.* 6, 1–13
51. Yang, J. *et al.* (2016) Drug delivery via cell membrane fusion using lipopeptide modified liposomes. *ACS Cent. Sci.* 2, 621–630
52. Hossen, M.N. *et al.* (2010) Ligand-based targeted delivery of a peptide modified nanocarrier to endothelial cells in adipose tissue. *J. Control. Release* 147, 261–268
53. Hossen, M.N. *et al.* (2012) Vascular-targeted nanotherapy for obesity: unexpected passive targeting mechanism to obese fat for the enhancement of active drug delivery. *J. Control. Release* 163, 101–110
54. Hossen, M.N. *et al.* (2013) A comparative study between nanoparticle-targeted therapeutics and bioconjugates as obesity medication. *J. Control. Release* 171, 104–112
55. Hossen, M.N. *et al.* (2013) Therapeutic assessment of cytochrome C for the prevention of obesity through endothelial cell-targeted nanoparticulate system. *Mol. Ther.* 21, 533–541
56. Hanley, M.J. *et al.* (2010) Effect of obesity on the pharmacokinetics of drugs in humans. *Clin. Pharmacokinet.* 49, 71–87
57. MacParland, S.A. *et al.* (2017) Phenotype determines nanoparticle uptake by human macrophages from liver and blood. *ACS Nano* 11, 2428–2443
58. Zhang, Y.N. *et al.* (2016) Nanoparticle–liver interactions: cellular uptake and hepatobiliary elimination. *J. Control. Release* 240, 332–348
59. de Jesus Felismino, C. *et al.* (2018) Effect of obesity on biodistribution of nanoparticles. *J. Control. Release* 281, 11–18
60. Park, Y.S. *et al.* (2010) Specific down regulation of 3T3-L1 adipocyte differentiation by cell-permeable antisense HIF1α-oligonucleotide. *J. Control. Release* 144, 82–90
61. Won, Y.W. *et al.* (2014) Oligopeptide complex for targeted non-viral gene delivery to adipocytes. *Nat. Mater.* 13, 1157–1164
62. Zhang, H.L. *et al.* (2012) Effects of chitosan and water-soluble chitosan micro- and nanoparticles in obese rats fed a high-fat diet. *Int. J. Nanomedicine* 7, 4069–4076
63. Rocca, A. *et al.* (2015) Pilot in vivo investigation of cerium oxide nanoparticles as a novel anti-obesity pharmaceutical formulation. *Nanomedicine* 11, 1725–1734
64. Thovhogi, N. *et al.* (2015) Targeted delivery using peptide-functionalised gold nanoparticles to white adipose tissues of obese rats. *J. Nanoparticle Res.* 17, 112
65. Zeng, W.S. *et al.* (2010) Bifidobacterium as an oral delivery carrier of oxyntomodulin for obesity therapy: inhibitory effects on food intake and body weight in overweight mice. *Int. J. Obes.* 34, 712–719
66. Thovhogi, N. *et al.* (2018) Peptide-functionalized quantum dots for potential applications in the imaging and treatment of obesity. *Int. J. Nanomedicine* 13, 2551–2559
67. Lacatusu, I. *et al.* (2019) Improved anti-obesity effect of herbal active and endogenous lipids co-loaded lipid nanocarriers: Preparation, in vitro and in vivo evaluation. *Mater. Sci. Eng. C* 99, 12–24

68. Sahuri-Arisoylu, M. *et al.* (2016) Reprogramming of hepatic fat accumulation and "browning" of adipose tissue by the short-chain fatty acid acetate. *Int. J. Obes.* 40, 955–963
69. Bagalkot, V. *et al.* (2015) Hybrid nanoparticles improve targeting to inflammatory macrophages through phagocytic signals. *J. Control. Release* 217, 243–255
70. Mingrone, G. *et al.* (2015) Bariatric–metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 386, 964–973
71. Esteban Varela, J. and Nguyen, N.T. (2015) Laparoscopic sleeve gastrectomy leads the U.S. utilization of bariatric surgery at academic medical centers. *Surg. Obes. Relat. Dis.* 11, 987–990
72. Kumar, R. *et al.* (2011) Fat malabsorption and increased intestinal oxalate absorption are common after Roux-en-Y gastric bypass surgery. *Surgery* 149, 654–661
73. Buchwald, H. *et al.* (2004) Bariatric surgery: a systematic review and meta-analysis. *Jama* 292, 1724–1737
74. Proietto, J. *et al.* (2013) Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program. *Ann. Intern. Med.* 144, 625
75. Colditz, G.A. *et al.* (2013) The effectiveness and risks of bariatric surgery. *JAMA Surg* 149, 275
76. Wolfe, B.M. and D'Alessio, D.A. (2016) Bariatric/metabolic surgery for diabetes: incorporating a powerful treatment into standard care. *Obesity* 24, 1205–1206
77. Morton, J.M. *et al.* (2017) American Society for Metabolic and Bariatric Surgery estimation of metabolic and bariatric procedures performed in the United States in 2016. *Surg. Obes. Relat. Dis.* 14, 259–263
78. Finks, J.F. *et al.* (2013) Surgical skill and complication rates after bariatric surgery. *N. Engl. J. Med.* 369, 1434–1442
79. Zeller, M.H. *et al.* (2015) Severe obesity and comorbid condition impact on the weight-related quality of life of the adolescent patient. *J. Pediatr.* 166, 651–659
80. Buncher, C.R. *et al.* (2015) Weight loss and health status 3 years after bariatric surgery in adolescents. *N. Engl. J. Med.* 374, 113–123
81. Inge, T.H. *et al.* (2017) Long-term outcomes of bariatric surgery in adolescents with severe obesity (FABS-5+): a prospective follow-up analysis. *Lancet Diabetes Endocrinol* 5, 165–173
82. Neovius, M. *et al.* (2018) Risk of suicide and non-fatal self-harm after bariatric surgery: results from two matched cohort studies. *Lancet Diabetes Endocrinol* 6, 197–207
83. Mechanick, J.I. *et al.* (2016) American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients With Obesity. *Endocr. Pract.* 22, 1–203
84. Narayanaswami, V. and Dwoskin, L.P. (2017) Obesity: current and potential pharmacotherapeutics and targets. *Pharmacol. Ther.* 170, 116–147
85. Rodgers, R.J. *et al.* (2012) Anti-obesity drugs: past, present and future. *Dis. Model. Mech.* 5, 621–626
86. Srivastava, G. and Apovian, C. (2018) Future pharmacotherapy for obesity: new anti-obesity drugs on the horizon. *Curr. Obes. Rep.* 7, 1–15
87. Kim, S.H. and Plutzky, J. (2016) Brown fat and browning for the treatment of obesity and related metabolic disorders. *Diabetes Metab. J.* 40, 12–21
88. Ghorbani, M. *et al.* (1997) Hypertrophy of brown adipocytes in brown and white adipose tissues and reversal of diet-induced obesity in rats treated with a β3-adrenoceptor agonist. *Biochem. Pharmacol.* 54, 121–131
89. Renz, C.L. *et al.* (2010) Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N. Engl. J. Med.* 363, 905–917