December 30, 2017

PharmacologyOnLine

Newsletter • 2017 • vol.3 • 27-34

CURRENT REVIEW ON MICROSPHERES AS DRUG DELIVERY CARRIERS FOR ANTI-DIABETIC, COLON TARGET AND ANTIHYPERTENSIVE DRUGS

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Abstract

Microspheres are free flowing proteins particles or synthetic polymers which are biodegradable in nature and crucial part of novel drug delivery system. It is a useful sustained or controlled drug delivery system for improving drug safety, better control of plasma drug level concentration, increase its residence time in the gastrointestinal with contact with the mucosa layer, reduce dosing frequency and improve patient compliance in addition to overcoming some of the disadvantages of conventional therapy. The formulations are more useful in chronic diseases condition including diabetes, hypertensive and GIT conditions. The purpose of the present review is to document current information on the use of microspheres over conventional dosage forms for anti-diabetic, colon target and antihypertensive drugs.

Keywords: *Microspheres, anti-diabetic drug, colon target drug, antihypertensive drugs.*

Introduction

Microspheres are as usual circular solid particle formation of proteins and synthetic polymers or polypeptide that are provided with a homogeneous drug delivery, prolonged the residence time drug release and eliminate gastric emptying [1, 2]. It is a crucial part of the novel drug and carrier associated drug delivery method and their particle size range is 1-1000 µm which are covered in core drug by polymers [3, 4]. A recent study has shown that most of the conventional dosage forms are providing a drug concentration fluctuation as a result drug pharmacological action suppressed. So they are required to formulate microspheres manner which is given a sustained or controlled release of drugs, resulting in diminished the fluctuations in the plasma drug levels and dosing frequency of administration [2, 3]. Several studies demonstrated that microspheres are proficient drug carrier particle, control the release rate or target the active drugs to a specific body absorption site for particulate drug delivery system, thereby it is improved drug absorption, reduced toxicity, superior patient compliance and convenience [5].

Therefore, the development of new controlled or sustained release of drug delivery system is one of the most excellent fields of research in pharmaceutical sciences which deliver the drug to the target tissue in the body. As a result, it has overcome difficult problems of conventional therapy such as drug toxicity, stomach irritation, resulting in enhanced the therapeutic efficacy of an administered drug and reduced toxicity [6]. Recently, some studies have reported that most of the conventional dosage forms are inferior biological half-life due to reducing patient's compliance. To overcome above problems, different types of controlled or sustained release dosage forms are formulated and altered which are increase patient compliance and biological half-life [7]. In recently proposed that controlled drug delivery system is to confirm the favorable most plasma drug concentration, consequently promote efficacy, safety, and bioavailability of drug with prosperous patient compliances [8]. Oral dosage forms such as enteric coated/ double-layer tablets are prepared to slow release the delivery of the drugs for 12 to 24 hours, but still, result in disabled systemic delivery of the drug and potential gastrointestinal tract irritation. Contrariwise, microcapsules are appointed to sustain drug release for oral use as a result in eliminates gastrointestinal irritation [9].

Currently exposed that drugs are achieved to deliver the active drug to a specific target tissue into the body in the optimal amount in the right period of time as a result of that low toxicity, negligible side effects and maintain the desired drug concentration [10]. Some studies shown that microspheres are provided controlling aspects of a drug given and uniform distribution of an active drug that facilitates the proper delivery of less amount of the potent drugs, with the clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug are highly affected by the behavior of the carrier [11]. In a recent study shown that microspheres are preparing dosage forms provided plenty concentration not only for sustained drug release but also for targeting of anticancer drugs to the specific site of a tumor [12]. Microspheres are promoted to release the drug slowly into the stomach, controlled or sustained the release rates and target drugs to a specific absorption site result in rapidly eliminated short half-life and increase gastric residence time[13].

The recent aim of this review is to study diverse aspects of the microspheres as drug delivery carriers for anti-diabetic, colon target and antihypertensive drug.

Anti-diabetic drug

Diabetes is a metabolic disease that is chronic hyperglycemia with troubles of carbohydrate, fat and protein metabolism resulting incompleteness produce insulin from pancreas organ. It has been reported that are affecting higher 220 million populations in the world and about 80% of diabetes patient deaths happen in low- and middle-income countries and the WHO estimates that the number of people will nearly be attacked 366 million in 2030 [13, 15]. Nowadays some studies have shown that anti-diabetic drugs are the major problem low biological half-life, poor bioavailability and decrease drug residence time and undesirable adverse effects. On the other hand, some researchers are considering a lot of benefits to make a novel drug delivery system to overcome antibiotics drug problems as well as metabolism problems [15].

Metformin is an anti-diabetic drug that is a main disadvantage short half-life (1.5-3 h) and low bioavailability (50±10 %). It is to prepare floating microsphere of Metformin hydrochlorides which may result in improved absorption and thereby increase the bioavailability of drug [16].Other studies have shown that metformin is first line treatment of type 2 diabetes and it is used in overweight, obese people, polycystic ovary syndrome and insulin resistance. The drug is given 2-3 times daily and needs to 1.5–3 g/day for maintaining effective plasma concentration. Metformin is to prepare oral sustained metformin formulation result in an increase in bioavailability as well as patient compliance [17]. Recently, studies found that glipizide is a second generation oral anti-diabetic drug used in type 2 diabetes which is stimulated the release of insulin from the pancreas into the body and lower the blood sugar level. It is low biological half- life (0.3+0.7 hours) and the drug is administered in 2 or 3 doses 2.5 to 10 mg per day.

Whereas glipizide is to make mucoadhesive microspheres that dosage forms are retained in the stomach result in raising the absorption, increase drug efficiency, reduce dose frequency and promote the biological half- life [18]. Repaglinide is an oral antihyperglycemic agent which is to prefer mucoadhesive microspheres formulation result in reducing dose frequency and control release of the drug. It is short biological half-life (1h) and low bioavailability (50%) [19, 24]. Recently, it has been proposed that nateglinide is provided to treat type 2 diabetes mellitus, lower blood glucose levels by blocking ATP- sensitive potassium channels in pancreatic beta cells, which stimulates insulin secretion. The usual dose of nateglinide is 60-120 mg three times a day. This drug is major problem short half-life (1.5 hours) low bioavailability (20-30%). It is to prepare floating microspheres which is achieved to prolong drug release and controlled drug delivery system [20, 21]. On the other hand, nateglinide is to make controlling blood glucose level and a formulated microsphere is to provide better control and improve patient compliance [22].

Currently, studies have been shown that Sitagliptin Phosphate is an insulin-sensitizing and model antidiabetic drug. It is a better half-life (8-14 h) and bioavailability (87 %) than other drugs. Sitagliptin is to make floating microspheres that is achieving sustained drug release in blood for a longer period of time result in improving absorption and thereby promote bioavailability [23].

Colon targeting drug

The colon specific drug delivery system is protecting the drug release and absorption in the stomach as well as small intestine and drug is distributed into the lower gastrointestinal tract result in decreasing dose frequency, lower side effects and increase patient compliance [25]. It is a specific site of local and systemic delivery of drugs that is to provide eradicating of different inflammatory bowel diseases such as ulcerative colitis, Crohn's disease, amebiasis, colon cancer and systemic delivery of protein and peptide drugs. The colon is poorly absorbed drugs and slower release rates or longer release due to a longer retention time of drugs in the colon thereby increasing bioavailability [26, 27].

Recently reported that the colon is a vascular organ and a site of specific drug delivery in the absorption site where the absence of digestive organ and long transit time result in improving systemic absorption of the drug and increasing bioavailability [28]. Review studies have shown that most of the drugs are in absorption sites in the small intestine but some other drugs are essential to be targeted to different absorption sites due to various factors like any disease disorder, degradation of drug situations, for sustained release of drugs etc. Contrariwise, the colon targeting of drugs are poorly soluble drugs in the absorption sites, inhibits the drug release in upper GIT and reducing the first pass metabolism of drugs [29]. Some studies have shown that most of the conventional dosage forms are prepared to target drugs into the colon but do not show sustaining or controlling drug release in the large intestine. In contrast, microspheres are the novel drug delivery system that confirms the sustained or controlled drug release into the colon targeting of drugs [30].

In recently, proposed that oral drug delivery systems are about 50% of drug delivery into the body and patients are easily receiving colon targeting of drugs caused by reducing dosage frequency, gastric irritation and improved patient compliance and bioavailability. The colon specific drug delivery systems (CDDS) are also used to anti-asthmatic, antihypertensive and antidiabetic drugs delivery in the colon [31]. Some studies proposed that CDDS microspheres are better than conventional dosage forms which result in more uniform drug dispersion in the large intestine, increases colon residence time and decreases local irritation [32].

Recent, studies showed that budesonide (BUD) is a glucocorticoid with high anti-inflammatory activity and it is used to treatment of inflammatory bowel disease. Budesonide is to develop microspheres for colon delivery that is acquiring sustained drug release, increase retention time and bioavailability, reducing dosing frequency, assuring the efficiency of treatment and improving patient compliance [33]. Indomethacin is an analgesic and non-steroidal anti-inflammatory drug which is used to prevent of rheumatoid diseases. It is a major problem short half- life (3-6). Indomethacin is to formulate the microspheres colon drug delivery system that is achieved to increase biological half-life [34]. It has been demonstrated that lornoxicam is an analgesic and non-steroidal anti-inflammatory drug that is used to efficient treatment of ulcerative colitis. It is to make microspheres colon targeting of drugs delivery result in improved bioavailability, maintaining plasma drug concentration and specific site of drug release in the body [35].

Currently, studies have been reported that Meloxicam is a NSAID (Non-steroidal anti-inflammatory drug) drug which is behavior treatment of colorectal cancer. Meloxicam is to prepare colon specific microspheres as a result of this drug is quickly released upper GI (gastrointestinal) tract and drug sustained 24 hours in lower GI tract at P^H 7.4 [36]. On the contrary, some studies have been shown that trimetazidine hydrochloride is an antianginal drug and it is main trouble low biological half-life (6±1.4h). It is formulated to colon targeting microsphere which is attaining site specific colon release and drug release up to 4-24 [37].

Nowadays, some studies found that levofloxacin (LFX) is a broad-spectrum antibiotic of the fluoroquinolone

drug class and short biological half- life (6-8). It is prepared to colon specific microspheres that are increasing half- life, decreasing side effects, ensuring the efficiency of treatment, improving compliance and reducing dosing frequency [38]. At present, studies have been reported that piroxicam is a non-steroidal anti-inflammatory drug that is used to treatment of rheumatoid arthritis. It comes with such as GIT irritation and slows drug release for about 10 hours at the site of absorption. But piroxicam colon specific microsphere is a good manner to achieve sustained release for about 24 hour and reducing side effects[39].

Antihypertensive drugs

Microspheres (novel drug delivery system) are a lot of opportunity for a formulation of antihypertensive drugs which are classified as ACE inhibitors, angiotensin antagonist, calcium channel blocker, diuretics, and vasodilator. Most of the antihypertensive drugs are being important drawbacks such as short half-life, low bioavailability, poor permeability and unwanted side effects. So Microsphere designs are achieved to overcome the disadvantage of hypertensive drugs [42]. Recently, studies have been showed that metoprolol tartrate is β-adrenergic receptor blocking agent which is used to treatment of mild to moderate hypertension and constant angina. It is a major drawback rapidly absorbed in gastric regions and patient compliance. Therefore, metoprolol tartrate microsphere is prepared to achieve prolong drug release, improve patient compliance, reduce dosing frequency and decrease side effects [43].

In the present study, losartan potassium is a desirable antihypertensive drug but is also used to plasma proteins, gastrointestinal disorders, neutropenia, acute hepatotoxicity, migraine, and pancreatitis. It is formulated to microspheres losartan potassium result in increasing biological half- life, reduce dosing frequency and in this manner reduce the drug resistance in patients. On the other studies have been showed that losartan is a better-sustained effect more than 12 hours [44, 45]. The study demonstrated that diltiazem HCl is an antihypertensive drug which is used to prevent angina pectoris and hypertension. It is a major problem short biological half- life (3-5 hour). Hence, diltiazem HCl is to develop microspheres as a result of a sustained release of drug up to 12 hours and increase half- life (about 14.8 hours) [46].

Conclusion

This review has shown the importance of sustained or controlled release drugs prepared using microspheres approach in pharmaceutical research. The significance of this method of formulation have been seen in anti-diabetic, colon target and antihypertensive drugs, which was seen in their increased therapeutic efficacy, biological half- life, reduce dosing frequency and improve patient compliance; hence, it could be considered as a novel drug delivery system which is more beneficial to patients than the conventional dosage form.

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Table 1: List of different oral anti-diabetic drug microspheres [16, 17, 18, 19, 20, 21, 22, 23, 24]

Drug	Polymers	Method used for preparation
Metformin Hydrochloride	Hydroxy propyl methyl cellulose (HPMC), Eudragit RS100	Emulsion solvent evaporation technique
Metformin Hydrochloride	Sodium alginate	Ionic gelation method
Glipizide	Carboxy methyl cellulose	Emulsification phase separation technique
Repaglinide	Carbopol, HPMC	Emulsification solvent evaporation technique
Nateglinide	Ethyl cellulose	Solvent evaporation method
Nateglinide	Ethyl cellulose, Eudragit S-100	Emulsion solvent evaporation method
Nateglinide	Olibanum gum and guar gum	Ionic gelation method
Sitagliptin Phosphate	Eudragit RS 100, HPMC	Solvent evaporation method

Table 2: Chart of various oral colon targeting of drugs microspheres [32, 33, 34, 35, 36, 37, 38, 39, 40, 41]

Drug	Polymers	Method used for preparation
Naproxen	Eudragit S-100, sodium alginate	Emulsification method
Budesonide	Guar gum.	Microspheres
Indomethacin	Eudragit L-100, Eudragit S-100	Solvent evaporation method
lornoxicam	Guar gum	Emulsification method
Meloxicam	Eudragit S-100, sodium alginate	Ionotropic gelation method
Trimetazidine hydrochloride	HPMC, Guar gum	Emulsification technique
Levofloxacin	Glutaraldehyde	Spray-drying method
Piroixicam	Sodium alginate, Eudragit S-100	Ionotropic gelation technique
Tinidazole	Eudragit L 100, Eudragit S 100	Solvent evaporation method
Diclofenac sodium	Ethyl cellulose, cellulose acetate phthalate (CAP), eudragit L 100-55.	Solvent evaporation technique

Table 3: List of different oral Antihypertensive drugs microspheres [43, 44, 45, 46, 47]

Drug	polymers	Method used for preparation
Metoprolol tartrate	Ethyl cellulose, polyethylene glycol-6000	Solvent evaporation method
Losartan potassium	Chitosan, sodium alginate	Solvent evaporation technique
Losartan	Ethylcellulose	Solvent evaporation manner
Diltiazem HCl.	Ethyl cellulose, Eudragit RS 100	Emulsion solvent evaporation technique
Atenolol	Hydroxyl propyl methyl cellulose, sodium alginate	Ionotropic gelation technique