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In vivo anti-obesity efficacy of curcumin loaded nanofibers transdermal patches in high-fat diet induced obese rats

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ABSTRACT

Obesity as a dominant problem in developed countries which is known to be basic step of so many diseases is subjected to find a solution for in this work. Curcumin containing polyvinyl alcohol-gelatin nanofibers which ranging from 200 to 250 nm in diameter as a transdermal drug delivery system for declining volume of subcutaneous adipose tissue is investigated here. Morphology and synthesis method of nanofibers is designed and optimized by statistical software and a totally uniform and reproducible method of synthesis is used for preparation of a transdermal patch. Effectiveness of delivery system in transport of drug through skin is confirmed by side by side arrangement transdermal diffusion cells. This transdermal patch used for animal test showed 4 to 7% decrease in total amount of adipose tissue estimated by whole body magnetic resonance imaging technique.

1. Introduction

Transdermal methods as a new delivery method for drugs started to attract attentions since 1980s [1]. This method of delivery has advantages over oral or injection method of delivery. It is less aggressive rather than injection and its advantage over oral delivery is that drug is not force to pass through harsh environment of gastrointestinal system. In addition, its spread over blood circularly system is less effected by liver and kidney function [1]. However, since that time, there are few examples of commercial transdermal drug delivery products. The major limitation of this delivery method is impermeability of most outer layer of skin called *stratum corneum*. For this reason, drug molecules used to be delivered should not be so large (400–500 Da) and a balanced lipophilicity (log octanol-water partition coefficient around 2 to 3 ideally) [2] is required for it to get into the blood stream. In addition, dose of drug required to be effective should not be so high [2].

Some drugs have been FDA approved to be used in transdermal delivery systems. Among them scopolamine (1979), glyceryl trinitrate (1981), clonidine (1984), estradiol (1986), fentanyl (1990), nicotine (1991), testosterone (1993), estradiol & norethisterone acetate (1998), norelgestromin & ethinyl estradiol (2001), estradiol & levonorgestrel (2003), oxybutynin (2003), selegiline (2006), methylphenidate (2006), rotigotine (2007), rivastigmine (2007) and granisetron (2008) are commercialized [2]. For heavier drugs and molecules which don't pass through skin easily, introduction of microneedles into transdermal patches has shown to be effective for a wide range of drugs and even vaccines since it bypass barrier layer mechanically [3, 4]. However, because of its moderate aggressiveness, in cases where drug delivery is possible without use of these semi aggressive methods, it seems to be preferable.

For treatment of obesity a wide range of treatments are advised. Some of them refer to change of lifestyle of patients which is the main cause of appearance of disease [5]. There is other type of methods including surgery which is very aggressive and in most cases reversible. Orally use of drugs which affects digestion of high calorie content of intake food has been approved by FDA. For example, Orlistat inhibits lipases in gastrointestinal system and prevents digestion of fats. However, it has its own side effects too. In searching for more effective method with less side effects, transdermal delivery treatment of obese mice have been studied using polymeric microneedle patches [6]. It is shown to be effective in decreasing volume of adipose tissue in diet induced obese mice. In addition, there are other effective drugs which use of them seems to be less aggressive. For example there are several phytochemical compounds which has been proved to effect as an anti-obesity agent on this type of tissue but for them to be effective high amount of them should be used orally due to kidney clearance function [7]. Resveratrol [8, 9], EGCG [10], genistein [11], and curcumin [12–16] are example of these phytochemicals which their metabolic function have been studied extensively.

As a drug which can target adipose tissue, curcumin, a yellow

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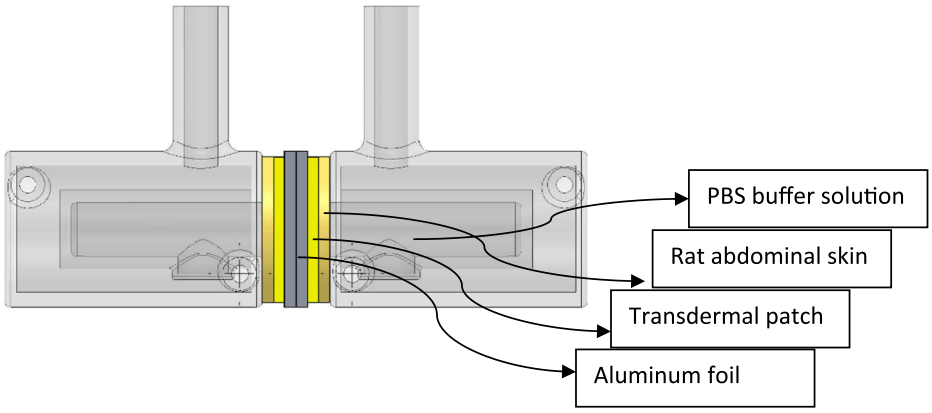

Fig. 1. Arrangement of side by side cells for transdermal diffusion test.

Table 1
Design parameter of screening model.

Run	Flow rate (ml/h)	Voltage (kV)	PVA %	Gel %	AA %	Distance (cm)	Drum speed (rpm)
1	1.20	15,000	4	15	5	20	100
2	1.20	25,000	4	8	5	8	100
3	0.30	15,000	1	8	5	8	–
4	0.30	15,000	4	8	15	20	–
5	1.20	25,000	1	8	5	20	–
6	0.30	15,000	1	15	5	20	100
7	0.30	25,000	4	15	5	8	–
8	1.20	15,000	1	8	15	8	100
9	0.30	25,000	4	8	15	20	100
10	1.20	15,000	4	15	15	8	–
11	1.20	25,000	1	15	15	20	–
12	0.30	25,000	1	15	15	8	100

Table 2
Statistical parameter of screening model.

Parameter	Sum of squares	Mean square	F value	p-Value Prob > F
Solvent percent in gelatin solution	922.77	922.77	5.06	0.0678
Mix ratio (PVA/gelatin)	3238.48	3238.48	5.39	0.0074
Distance	1.40	1.40	18.93	0.9315
voltage	15.62	15.62	8.156E−003	0.7747
Drum speed	363.64	363.64	0.091	0.2047
Flow rate	648.90	648.90	2.13	0.1090
Model	5190.80	171.08	3.79	0.0480

phytochemical compound extracted from some type of traditional mushroom in china, is known to be effective to treatment of various physiological problems related to this tissue. Its effects as an anticancer [17, 18] product is proven and acts as anti-inflammatory and anti-obesity drug [19].

For enhancement and control of drug delivery by transdermal method, various systems have been used. Use of thin polymer films as a layer on the skin was the first method for preparing delivery system [2]. However, for increasing the rate of delivery and decreasing time required to reach to a steady state, use of nanostructured materials is an option. Nanoparticles in different systems like liposomes [20], transfersomes [21], and many different nanostructured materials [1] have been used to increase the obtain better delivery results. Use of nanofibers as a nanostructures system for transdermal drug delivery is rarely reported [22, 23]. Use of nanofibers in transdermal delivery systems has advantages; low diameter of fibers increased the rate of drug diffusion from inside of fiber matrix to the surface of skin, obtaining very uniform distribution of drug and high repeatability of release profile gives a better control of synthesis in comparison to other nanostructured systems.

In this work, we used a blend of gelatin/albumin and PVA for entrapment of curcumin to obtain a transdermal delivery patch. PVA based nanofibers are previously investigated by some authors [24–26]. Blend of gelatin and curcumin is previously reported to be synthesized by electrospinning [27–29]. Here, we screened parameters in synthesis of fibers and selected the most effective parameters and then optimized fiber quality via controlling of synthesis parameters using sets of data. Using optimum point achieved by this method, drug delivery system to be tested ex vivo and in vivo for transdermal delivery and effectiveness in decreasing adipose tissue mass in rats. Weight profile of animals followed for each group in period of experiment. In addition to estimation of volume percent of adipose tissue by MRI imaging were used to confirm effectiveness of drug delivery system. Estimation of concentration of some obesity related metabolites in blood plasma used to confirm effectiveness of this delivery system to take drug molecule to target tissue.

2. Materials and methods

2.1. Materials

Bio-degradable PVA (poly vinyl alcohol) (MV = 89,000 to 98,000 and 99+% hydrolyzed) and analytical grade gelatin was purchased from were purchased from Sigma-Aldrich (USA). All reagents and chemicals were purchased from Merck. Curcumin was purchase from Sigma-Aldrich.

2.2. Screening electrospinning parameters for preparation of nanofiber

The electrospinning of nanofibers was performed by an instrument made by Fanavaran Nano Meghias Company, IRIB. Condition for electrospinning was designed by design expert software based on Placket-Berman method. Twelve different conditions with various voltage, PVA concentration, gelatin concentration, formic acid concentration, distance between tip of needle and collector, injection speed and drum speed were used for preparation of nanofibers and SEM images of them were captured by Serontechnologies AIS2100 instrument in Amirkabir University, Tehran, Iran. Factors extracted from images used as response to analyze nanofiber synthesis method. These factors were diameter, diameter standard deviation, pore size, pore size standard deviation and porosity.