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Original Article

Customizing the Protoscolicidal Activity by a Drug Delivery System: Application of Guar Gum in Electrospun Nanofibers

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Abstract

Background: The present study aimed to control mebendazole drug release from ethyl cellulose nanofibers containing guar gum produced by Electrospinning Method (ESM) on mortality of hydatid cyst protoscoleces under laboratory conditions.

Methods: The study was conducted in Arak Islamic Azad University, 2019. After preparation of ethyl cellulose nanofibers containing guar gum with concentrations 10, 250, 50 and 500 ppm with ESM, the uniformity and fineness of nanofibers were investigated by electron microscope. By determining the absorption of nanofibers during 312 h via spectrophotometry method, the amount of drug release was obtained. Then, the mortality of live protoscoleces in-vitro with nanofibers made with different concentrations was studied during 13 days.

Results: Guar gum nanofiber with four concentrations of 10, 50, 250 and 500 ppm had 0.78512, 0.83729, 1.0098 and 1.0633 absorption respectively and showed drug release 42.09%, 39.95%, 33.05% and 30.96% after 312 hours. Therefore, the survival of protoscoleces in the presence of guar gum with four concentrations was zero after 3, 6, 11 and 13 days ($P<0.05$).

Conclusion: To produce nanofibers carrying the drug for research related to the treatment of hydatid cysts, the electrospinning technique can be considered as a reliable method.

Introduction

Hydatidosis is one of the most important zoonotic diseases caused by *Echinococcus granulosus*. The larval stage of this parasite, *E. granulosus*, in internal organs of herbivores and humans, leads to the formation of a single-cavity hydatid cyst. This

parasite mostly invades body' tissues, including liver, lung, kidney, heart, bones (mostly in spine), brain, and other organs of the body. However, the most at risk organs are liver (50%-75%) and lungs (18%-30%). If the disease is detected early enough, it can be successfully treated; otherwise, cysts are twisted so complicate the treatment. The major risk of this disease is that it may be asymptomatic in the body for many years, and once symptoms appear, recurrent dangerous cysts are formed (1-4).

Human infection with parasites has been known as one of the health problems of the world from the very distant past. Currently, surgery is a selective treatment for single-cavity hydatid cysts (4-8). However, several patients cannot be candidates for surgery due to multiple lesions in different organs or due to specific physical conditions. On the other hand, the results of surgical procedures have not always been successful, and in some cases, they have been associated with secondary dissemination and local recurrence. In these cases, treatments are used. Commonly used drugs from the benzimidazoles group include albendazole and mebendazole for which different effectiveness has been reported in various studies (9).

In recent years, Electrospinning Method (ESM) has been used as a highly advanced technology for the production of electrostatic nanofibers. It has proven to be very promising in the field of drug release in medicine (10-13). In ESM, recently evolved considerably, applying an electric force, a polymer solution is used to produce nanofibers with diameters between 2 nanometers to several micrometers (14, 15). Mebendazole is a selective drug that results in protoscoleces death with a half-life of about 5 h at a dose of 100 mg once a day by reducing the glycogen stores in cells. To control mebendazole drug release, guar gum has been used with many applications in the field of drug release in medicine (16, 17). Since treatment methods used to treat hydatid cyst do not offer a desirable performance in some cases, we decided to destroy hydatid cyst protoscoleces via an efficient and modern method called electrospinning under laboratory conditions.

We aimed to evaluate mebendazole drug release from nanofibers containing guar gum produced by electrospinning method on the mortality of hydatid cyst protoscoleces under laboratory conditions.

Materials and Methods

Preparation of guar gum fiber by an electrospun machine

The study was conducted in Arak Islamic Azad University, 2019.

Mendazole and guar gum had been developed by Modava and Parsin Exir Company and ethylcellulose by an American Company named Aldrich. A polymer solution containing 2 mg mebendazole, 500 mg ethanol, 4500 mg ethylcellulose, and different concentrations of guar gum 10, 50, 250 and 500 ppm was placed on a metal plate called collector. The plate was fixed to the ground and a syringe was placed on a pump. The needle was connected to a high voltage power supply where the solution flowed to the syringe at a low flow rate. When the voltage was applied between 5 and 30 kW, the drop stretched along the path like a jet. Once the solvent evaporated, it hit the metal plate, and then was collected as a nanostructure fiber from a metal plate. When producing the intended nanofiber, ethylcellulose with 1:9 ratio of ethanol was placed in an ultrasonic device for about half an hour. Next, about 0.002 g mebendazole drug was added to the solution along with 0.5 ml of each controller with specific concentrations. The prepared solution was transferred to 5 cc syringe and machine operated at 700 rpm, 0.5 ml / h, 15 kw; after 6 h, the intended fiber was extracted (Fig. 1).

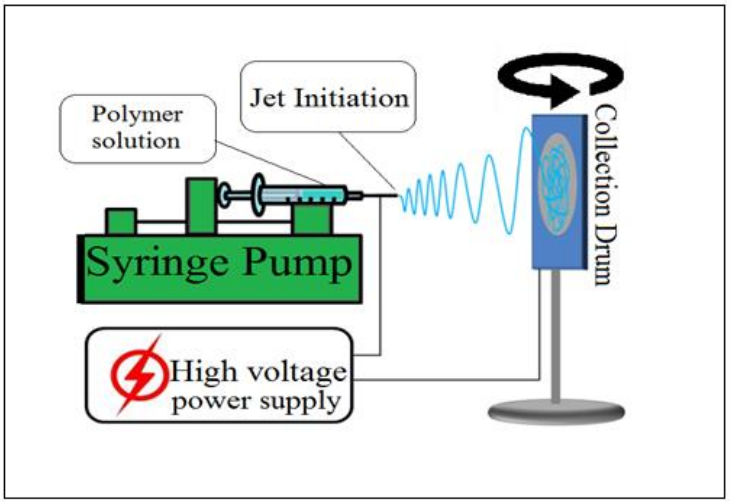

Fig. 1: Schematic setup of Electrospinning

Scanning Electron Microscopy (SEM)

Nanofibers produced by ESM were prepared for photographing by an electron microscope via SEM method, and Phenom ProX model with a magnification range up to 130,000 times and an image resolution equal to14 nm. In this study, two groups of nanofibers were made. Figure 2 presents the nanofiber containing ethylcellulose without drug and controller (guar gum) (2a) as well as nanofiber containing ethylcellulose with 0.002 g drug and 0.5 cc controllers (2b).

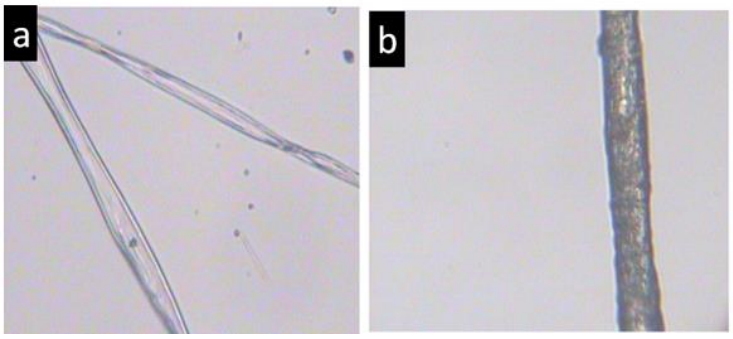

Fig. 2: a) nanofiber containing ethyl cellulose made with electrospinning method, **b)** nanofiber containing ethyl cellulose, 0.002 g drug and 0.5 ml controller made with electrospinning method

Producing guar gum nanofiber

To synthesize a fine and uniform nanofiber capable of carrying the drug and controller, the conditions of 700 rpm and 10% weight should have been maintained (Fig.3a). Otherwise, the fiber would be thickened and tied, and no good uniformity could be obtained (Fig.3b). In other words, it could not be a suitable carrier for carrying the drug and controller.

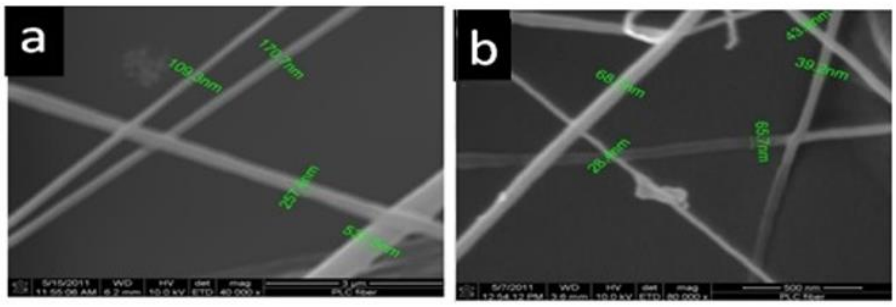

Fig. 3: SEM micrographs of ethyle cellulose / various proportions controller nanofibers varying in solution concentration at collector rotating speed : **a)** 700 RPM , 10 wt% **, b)** 300 RPM, 15 wt%

Preparing blank for nanofibers and test samples

Preparing blank

About 10 mg was extracted from fibers without drug, which contained ethyl cellulose and guar gum as controller with different concentrations (10, 50, 250 and 500 ppm). They were then brought to the volume in a 10-cc flask with a physiological serum whereby a special blank was provided for each fiber.

Preparing test samples

About 10 mg was withdrawn from fibers with mebendazole drug, guar gum with different (10, 50, 25 and 500 ppm) concentrations and ethyl cellulose, brought to the volume in a 10 ml flask with physiological serum.

UV Analysis for blank and sample test

Nanofibers produced by ESM method were subjected to spectrophotometry method with Hewlett-Packard 8453 device characteristics to determine the best absorption and release percentage. Blank absorption and samples were taken from zero to 312 h using a quartz cell with a wavelength of 234 nm and wave amplitude of 200-500 to obtain the best absorption. The absorption revealed significant changes over time. For each sample, the relationship between absorption number and released drug concentration was determined by plotting a calibration curve. Since the amount of drug used in each nanofiber was known, the percentage of drug release could be determined by calculating the proportion of the released drug to the entire drug used in each fiber.

Preparation of hydatid cyst protoscoleces

The livers infected with hydatid cyst of slaughtered domestic livestock were prepared from the industrial slaughterhouse of Arak city - Markazi province (8) (Fig. 4). They were immediately transferred to the laboratory of parasitology at Faculty of Medicine, Arak University of Medical Sciences, Markazi, Iran. The cysts were washed 3 times with saline buffer phosphate solution (PBS, ph= 7.2) and then protoscoleces were extracted under hood and sterile conditions using the method previously described. The percentage of protoscoleces viability was determined as 0.1% by eosin with sterilized cap tubes containing protoscoleces being centrifuged for 10 min at 2000 rpm. Once the protoscoleces precipitated in the RPMI medium, they were transferred into a 37 °C Incubator.

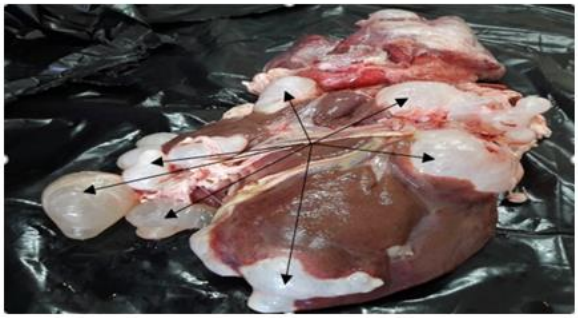

Fig. 4: Liver of sheep infected with hydatid cyst

Determining the viability of protoscoleces

To calculate the mortality rate of protoscoleces, 0.1% eosin solution, as well as 10 and 40 lens optical microscope, were used. After staining, live protoscoleces remained colorless and had cellular contractions plus moving flame cells. However, the dead protoscoleces absorbed eosin color and turned into red (Fig. 5). In this study, samples with protoscoleces over 90% were selected for evaluation of drug release (18).

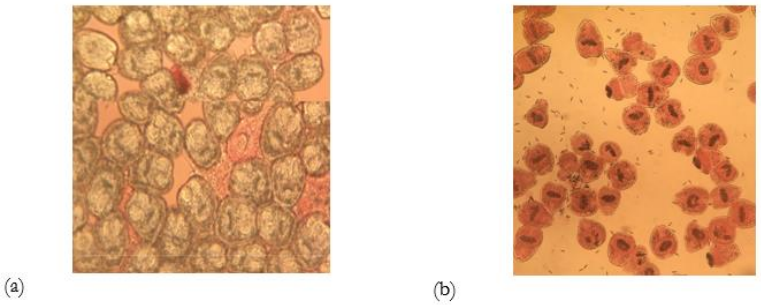

Fig. 5: Exposing protoscoleces to 0.1% eosin with × 40 optical microscopes. **a)** Live protoscoleces on the first day, **b)** 100% killed protoscoleces on day 13 in the presence of fiber containing 500 ppm guar gum

Measuring the mortality of protoscoleces by nanofibers over a period of 13 days

In order to investigate the guar gum control in nanofibers on mebendazole drug release for mortality of protoscoleces, nanofibers examined by spectrophotometry method were transferred to the parasitological laboratory of Faculty of Medicine at Arak University of Medical Sciences. The mortality of protoscoleces maintained at 37 °C was examined for 13 days (Table 1).

Table 1: Anofibre components and fluid properties of hydatid cyst in the tests

Groups name	*Guar gum*	*Mebendazole*	*Ethyl cellulose*	*Protoscoleces*	*RPMI medium*
Groups 1	10 ppm	0.002 g	4500 mg	20 λ	8 cc
Groups 2	50 ppm	0.002 g	4500 mg	20 λ	8 cc
Groups 3	250 ppm	0.002 g	4500 mg	20 λ	8 cc
Groups 4	500 ppm	0.002 g	4500 mg	20 λ	8 cc
Control group 1	-	0.002 g	4500 mg	20 λ	8 cc
Control group 2	-	-	4500 mg	20 λ	-

Ethical statement

All experimental procedures were approved by the Ethics Committee of Islamic Azad University of Arak (No. 12130307942002).

Statistical analysis

We used ANOVA test for analysis and $P<0.05$ was considered for significant differences.

Results

After analyzing the absorption of nanofibers over a period of 13 d by spectrophotometry method, the graphs of nanofiber absorption and release percentage over time were plotted (Fig. 6 and 7).

After studying mortality of protoscoleces over a period of 13 d in the laboratory environment, the viability graph of protoscoleces in the absence of and in the presence of guar gum controller overtime was plotted (Fig. 8).

The highest absorption and percentage of drug release were associated with nanofibers containing 10 ppm guar gum, while the lowest absorption and percentage of drug release were associated with nanofibers containing 500 ppm guar gum. Moreover, according to Fig. 8, the protoscoleces' mortality within the shortest and longest times was associated with nanofibers containing 10 ppm guar gum and 500 ppm guar gum, respectively. There was a significant difference between variances confirmed by Tukey's test (P<0.05).

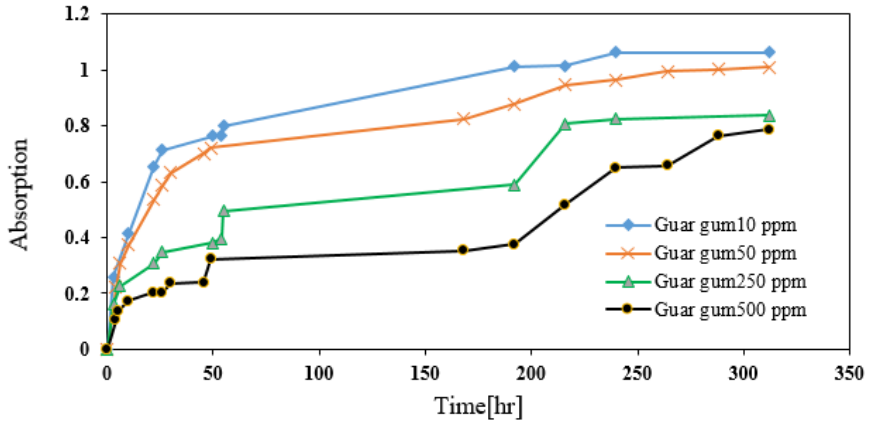

Fig. 6: Absorption of nanofibers containing mebendazole drug, ethyl cellulose and guar gum with different concentrations to time

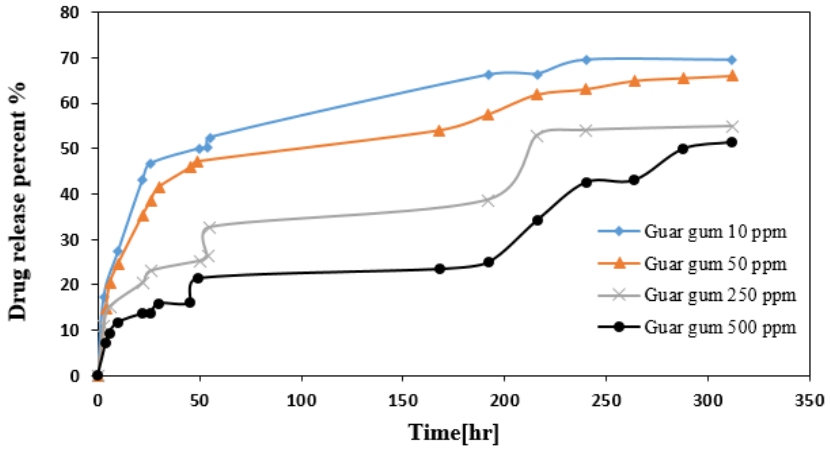

Fig. 7: Percentage of mebendazole drug release from nanofibers containing mebendazole drug, ethyl cellulose and guar gum with different concentrations to time

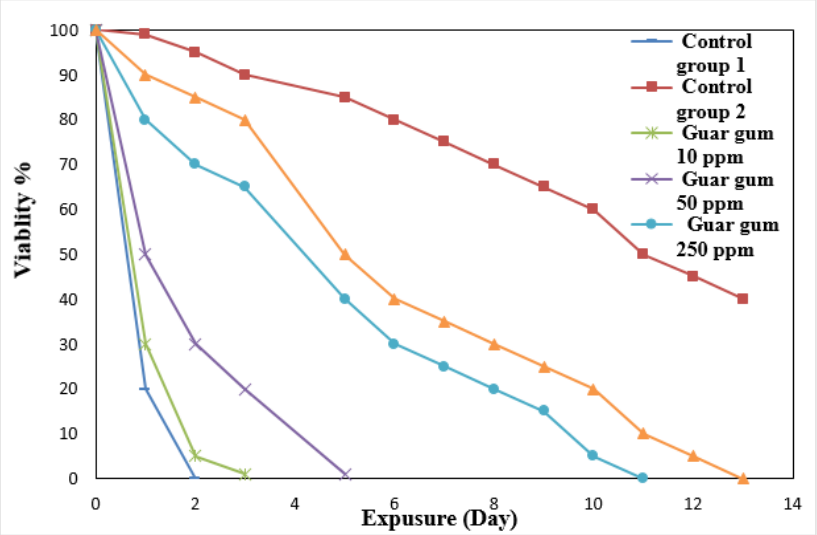

Fig. 8: Effect of nanofibers containing ethyl cellulose, mebendazole drug, and guar gum controller with different concentrations in RPMI medium in the presence of hydatid cyst protoscoleces over a period of 13 days. Each percent represents the average percentage of live protoscoleces

Discussion

Several treatment methods have been proposed to eliminate this parasite Including chemical drugs and herbal drugs and magnetic fields, with the most effective one being surgery. However, unfortunately, the possibility of tearing cysts during surgery and disease recurrence is high. Another method of treatment is the use of albendazole and mebendazole tablets recommended 3 months before surgery and 1-3 months post-surgery (6, 19, 20).

The use of medication in the treatment of hydatidosis is helpful; however, excessive consumption of these drugs may have dangerous complications. In traditional medicine, many herbal medicines have also been introduced, but they have not been taken into account due to their inefficiency (21). Electrospinning is an advanced technology for producing nanofibers, proven to be very interesting in the field of drug release in medicine (22-24) and pharmaceutics including the production of polar and nonpolar drugs, as well as water-soluble and insoluble drugs used for treatment of topical eye diseases, spinal cord problems and angina control (24-26), high blood pressure (27), and Alzheimer's disease (28). According to the above-mentioned studies, no significant study has been conducted on the use of nanofibers produced by ESM on hydatid cyst protoscoleces so far. In this study, mebendazole drug was used for inducing mortality of hydatid cyst protoscoleces while guar gum was employed for controlling drug release. Guar gum along with nanofibers containing drug have been taken into account for treatment of cancers, especially colorectal cancer, cholera, constipation, diarrhea, modulating appetite, dry eye, and blood glucose control (29-34). In ESM, fibers are produced in a nanoscale range. Drug release can be purposefully controlled by loading the drug and controller on the produced nanofibers (22, 23, 35, 36). In this method, nanofibers should be designed in a uniform and fine viscoelastic structure. Creating a strong electric field (15 kw), enhancing electrical conductivity, obtaining 700 rph proper speed using ESM, and gaining 10% weight concentration of ethyl cellulose solution and drug were performed towards

this goal to uniformly distribute the drug and controller on nanofibers (Figs. 2 and 3). In other words, the controller and drug were distributed throughout the nanofiber. Upon the increase in the viscosity of the solution due to the presence of controller and drug, the hardness and diameter of the nanofiber increased. All fibers without controller had the same morphology. However, in the presence of controllers, their structure varied. In this study, nanofibers with four different concentrations of guar gum controller (10, 250, 50, and 500 ppm) were made, and their uniformity and tie-freeness were photographed and confirmed by an electron microscope with a magnification of 130000 times (Fig. 2).

In recent studies on drug release in the medical field, intestine-targeted tablets have been produced using different concentrations of guar gum. Guar gum was used as the controller of mebendazole drug release in the production of intestinal pills. There was no chemical interaction between mebendazole drug and guar gum. Since in the above-mentioned study, more than 90% of the drug was released within 12 h, guar gum technology was not well used to control mebendazole drug release (37, 38). However, in our study, mebendazole drug release behavior was examined in different formulations using ESM, such that mebendazole drug release was adjusted to 312 hours. In other words, protoscoleces' mortality conditions can be effectively provided using lower mebendazole drug doses (0.002 g). In another study, intestinal pills and high doses of guar gum polymer (20% and 30%) were used to control mebendazole drug release (38). On the other hand in our study, using a very low dose of mebendazole drug (0/002 g) and guar gum (25×10^{-5}) in nanofibers, mebendazole drug release was effectively controlled.

In this study, the amount of drug released in the environment and the percentage of nanofiber release were obtained through determining the absorption of nanofibers via spectrophotometry. Each nanofiber had its absorption rate, where guar gum nanofiber with 4 concentrations (10, 50, 250, 500 ppm) had (0.78512, 0.83729, 1.0098 and 1.0633) absorptions, respectively and showed 42.09%, 39.95%, 33.05%, 30.96%) drug release percentage after 312 h, respectively. In other words, as the guar gum concentrations in nanofiber diminished, the absorption amount of nanofiber, released drug into the environment, and drug release percentage increased where the mortality of protoscoleces grew accordingly as well (Figs. 6 and 7). In this regard, guar gum with 4 (10, 50, 250, 500 ppm) concentrations led to complete protoscoleces' death after 3, 6, 11, and 13 d, respectively. Indeed, guar gum used in the nanofiber can be a great agent in controlling mebendazole drug release and hydatid cyst protoscoleces' mortality. The mortality of protoscoleces was observed in control group 1 within 2 days. The low mortality rate of protoscoleces can be attributed to the lack of controller in nanofibers. However, in control group 2, protoscoleces' mortality rate was reported 60% due to a lack of medication (drug) over 13 days. The considered nanofibers alone are not the cause of protoscoleces' death (Fig. 8). In this study, we tried to remove hydatid cyst protoscoleces through synthesizing a suitable nanofiber via electrospinning method. We hope our findings will be used as a problem-solving approach for the treatment of hydatid cyst disease in further studies.

Conclusion

After the production of nanofibers with ESM, and the confirmation of their uniformity and fineness by electron microscopy, the absorption rate of all nanofibers was obtained using spectrophotometry method. Guar gum can be used as a controller drug release. In other words, by changing the concentration of guar gum used in nanofibers, the rate of absorption, drug release, and finally mortality of protoscoleces will change. The electrospinning

technique can be used as an effective step in treating hydatid cysts.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Abedi B, Maghsood A, Khansarinejad B, et al. Genotyping of *Echinococcus granulosus* isolates from livestock based on mitochondrial cox1 gene, in the Markazi province, Iran. J Parasit Dis. 2019;43(4):592-596.
2. Fathi S, Ghasemikhah R, Mohammadi R, et al. Seroprevalence of Hydatidosis in People Referring to Reference Laboratory of Gorgan, Golestan Province, Northern Iran 2017. Iran J Parasitol. 2019;14(3):436-443.
3. Ghasemikhah R, Shahdoust M, Sarmadian H, et al. *Echinococcosis* in livestock slaughtered in arak industrial abattoir in Central Iran during 2006 to 2012. West Indian Med J. 2015.
4. Sabzevari S, Badirzadeh A, Shahkaram R, et al. Traumatic rupture of liver hydatid cysts into the peritoneal cavity of an 11-year-old boy: a case report from Iran. Rev Soc Bras Med Trop. 2017 Dec;50(6):864-867.
5. Karimi M, Ghasemikhah R, Mirahmadi H, et al. Discrimination of Mixed Infections of *Echinococcus* Species Based on in Silico Sequence Analysis: A New Way of Reflecting Overlapped Strains in Indigenous Areas. Arch Clin Infect Dis. 2017;12(4):e14168.
6. Ebrahimi A, Assadi M, Saghari M, et al. Whole body bone scintigraphy in osseous hydatosis: a case report. J Med Case Rep. 2007;1:93.
7. Hajihossein R, Eslamirad Z, Mosayebi M, et al. In vitro effects of vinegar on protoscolices of hydatid cyst. Asian Pac J Trop Dis. 2015;5(3):210-213.
8. Valizadeh M, Haghpanah B, Badirzadeh A, et al. Immunization of sheep against *Echinococcus granulosus* with protoscolex tegumental surface antigens. Vet World. 2017;10(8):854-858.
9. Ghasemikhah R, Tabatabaiefar MA, Shariatzadeh SA, et al. A PCR-Based Molecular Detection of *Strongyloides stercoralisin* Human Stool Samples from Tabriz City, Iran. Sci Pharm. 2017;85(2):17.
10. Luo W-L, Qiu X, Zhang J, et al. In situ accurate deposition of electrospun medical glue fibers on kidney with auxiliary electrode method for fast hemostasis. Mater Sci Eng C Mater Biol Appl. 2019;101:380-386.
11. Mo X, Sun B, Wu T, et al. Electrospun Nanofibers for Tissue Engineering. In. Electrospinning: Nanofabrication and Applications: William Andrew Publishing; 2019. p. 719-734.
12. Nagarajan S, Bechelany M, Kalkura N, et al. Electrospun Nanofibers for Drug Delivery in Regenerative Medicine. In. Applications of Targeted Nano Drugs and Delivery Systems: Elsevier; 2019; 595-625.
13. Chen S, Li R, Li X, et al. Electrospinning: An enabling nanotechnology platform for drug delivery and regenerative medicine. Adv Drug Deliv Rev. 2018;132:188-213.
14. Fu Y, Liu L, Cheng R, et al. ECM decorated electrospun nanofiber for improving bone tissue regeneration. Polymers (Basel). 2018;10(3):272.
15. Sapountzi E, Braiek M, Chateaux J-F, et al. Recent Advances in Electrospun Nanofiber Interfaces for Biosensing Devices. Sensors (Basel). 2017;17(8):1887.
16. Patel J, Karve M, Patel NK. Guar gum: a versatile material for pharmaceutical industries. Int J Pharm Pharm Sci. 2014;6(8):13-19.
17. Thombare N, Mishra S, Siddiqui M. Guar gum as a promising starting material for diverse applications: A review. Int J Biol Macromol. 2016;88:361-372.

18. Badirzadeh A, Raeghi S, Fallah-omrani V, et al. Cryopreservation of *Echinococcus granulosus* Protoscoleces. Iran J Public Health. 2020;49(1):181-5.
19. Dalimi A, Ghasemikhah R, Hashemi Malayeri B. *Echinococcus granulosus*: lethal effect of low voltage direct electric current on hydatid cyst protoscoleces. Exp Parasitol. 2005;109(4):237-240.
20. Sarmadian H, Ghasemikhah R, Mirmoradi F. The Toxic Effect of Magnetic Field on Protoscoleces of Hydatid Cyst in Vitro. Iranian J Toxicol. 2013;7(22):926-931.
21. Mahmoudvand H, Dezaki ES, Kheirandish F, et al. Scolicidal effects of black cumin seed (*Nigella sativa*) essential oil on hydatid cysts. Korean J Parasitol. 2014;52(6):653-9.
22. Sasmal P, Datta P. Tranexamic acid-loaded chitosan electrospun nanofibers as drug delivery system for hemorrhage control applications. J Drug Deliv Sci Technol. 2019;52:559-567.
23. Khoshnevisan K, Maleki H, Samadian H, et al. Cellulose acetate electrospun nanofibers for drug delivery systems: Applications and recent advances. Carbohydr Polym. 2018;198:131-141.
24. Sasikanth K, Nama S, Suresh S, et al. Nanofibers-A New Trend In Nano Drug Delivery Systems. The Pharma Innovation. 2013;2(2, Part A):118.
25. Cui W, Zhou Y, Chang J. Electrospun nanofibrous materials for tissue engineering and drug delivery. Sci Technol Adv Mater. 2010;11(1):014108.
26. Hamori M, Yoshimatsu S, Hukuchi Y, et al. Preparation and pharmaceutical evaluation of nano-fiber matrix supported drug delivery system using the solvent-based electrospinning method. Int J Pharm. 2014;464(1-2):243-251.
27. Akhgari A, Shakib Z, Sanati S. A review on electrospun nanofibers for oral drug delivery. Nanomed J. 2017;4(4):197-207.
28. AnjiReddy K, Karpagam S. Chitosan nanofilm and electrospun nanofiber for quick drug release in the treatment of Alzheimer's disease: In vitro and in vivo evaluation. Int J Biol Macromol. 2017;105(Pt 1):131-142.
29. Bhardwaj N, Kundu S. Electrospinning: a fascinating fiber fabrication technique. Biotechnol Adv. 2010;28(3):325-347.
30. Gorji M, Bagherzadeh R, Fashandi H. Electrospun nanofibers in protective clothing. Electrospun Nanofibers. 2017; 571-598.
31. Weiss J, Kanjanapongkul K, Wongsasulak S, et al. Electrospun fibers: fabrication, functionalities and potential food industry applications. Nanotechnology in the Food, beverage and nutraceutical industries: Elsevier; 2012; 362-397.
32. Chen S, Boda SK, Batra SK, et al. Emerging Roles of Electrospun Nanofibers in Cancer Research. Adv Health Mater. 2018;7(6):e1701024.
33. Liu F, Chang W, Chen M, et al. Film-forming properties of guar gum, tara gum and locust bean gum. Food Hydrocoll. 2020;98.
34. Anandan D, Madhumathi G, Nambiraj NA, et al. Gum based 3D composite scaffolds for bone tissue engineering applications. Carbohydr Polym. 2019;214:62-70.
35. Eslamian M, Khorrami M, Yi N, et al. Electrospinning of highly aligned fibers for drug delivery applications. J Mater Chem B. 2019;7(2):224-232.
36. Topuz F, Uyar T. Electrospinning of Cyclodextrin Functional Nanofibers for Drug Delivery Applications. Pharmaceutics. 2018;11(1):6.
37. Baviskar D, Rajput A, Bare K, et al. Development and in vitro characterization of mebendazole delayed release tablet for colonic drug delivery. Pak J Pharm Sci. 2014;27(2):249-53.
38. Krishnaiah Y, Raju PV, Kumar BD, et al. Development of colon targeted drug delivery systems for mebendazole. J Control Release. 2001;77(1-2):87-95.