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RESEARCH ARTICLE

Automatic Control of Microfluidic Flow Using Natural H ydrogels

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Abstract

Objectives: To explore the effectivity of natural hydrogels for controlling the microfluidic flow in smart bandages. Worldwide, several researchers are trying to develop smart bandage having the capabilities of controlled amount of automatic drug flow to the wound, but the complexity of the required mechatronics does not allow the size of the bandage to be easily wearable. **Method:** The drug flow within the microchannels of the bandage is controlled using easily available hydro sensitive seeds (*Plantago ovato* and *Salvia hispanica* L). On placing the seeds within the microchannels, the investigations showed that the water content within the drug is slowly absorbed by the seeds and the flow of drug is restricted within the channel leading to the controlled flow in a small passage of time. **Findings:** *Plantago ovato* and *Salvia hispanica* L. as natural hydrogels show effective control of the flow rate required for smart bandages. The analysis of the results shows that *Salvia hispanica* L. can efficiently be used for controlling the drug flow within the microchannels and *Plantago ovato* for absorbing residue within the sink of the bandage. **Novelty:** The main problem of the smart bandages developed in some of the labs is the complexity of the design used for controlling the drug flow. The novelty of the proposed smart bandage is its low cost design and efficiency of automatic regulating drug flow without the use of complicated electronics.

Keywords: Hydrogels; fluid control; microfluidic; drug reservoir; smart bandage

1 Introduction

The recent decades have seen a sharp increase in development of smart bandage systems for wound healing throughout the world. The wound physiology may be determined by various factors like temperature, oxygen, moisture, and pH. A deviation of 2.2^{0}C in temperature is a sign of worsening of the wound. Several wound specific bandages have been reported by the researchers worldwide. Artem et al have reported a wireless bandage for diabetic patients that consist of a printed flexible wireless stimulator. The directional energy supplied to the wound helps in healing the wound fast in diabetic patients[1–4]. The main requirement of the smart bandage is to stop the flow of drugs to the wound after a specific estimated time. Only two methods may be used for achieving it. The first one is the use of mechatronics components, but that may result in massive and expensive structure of bandage which seems to be unrealistic. The other alternative is the use of hydrogels in smart bandages to regulate the flow which is economical and an ergonomic design of the bandage may be developed. Hydrogels are the emerging material finding their use in smart bandage industry. The hydrogel is a three-dimensional network of hydrophilic natural polymers and gums having the capacity to retain large quantities of water. Hydrogels are broadly classified into two types as natural and synthetic hydrogels. The similarities between natural and synthetic hydrogels, their high water content flexibility, and porosity open the door for hydrogel-based medical research. Different flow control methods have been reported by researchers worldwide for manipulating the fluid flow in microfluidics. Fabricated natural and synthetic hydrogels may serve as a substitute for controlling the flow of fluid in microfluidic channels and smart bandages. Natural hydrogels are emerging biomaterials with applications in biotechnology, tissue engineering, and chemical engineering. These show promising results in tissue engineering as compared to synthetic hydrogels that may cause side effects resulting in complications. Natural hydrogels are fabricated using modern bioprinting technologies to overcome the drawbacks of conventional fabrication methods. Tissue engineering is a complex phenomenon for the formation of biological structures/ tissues that are put to human use so that body's immune system hardly differentiates between the original tissue and fabricated tissue. Fabrication of complex human tissues requires biodegradable and biocompatible frameworks of natural hydrogels. Natural hydrogels are being embedded with modern fabrication techniques to make these compatible for use in tissues [5]. Hydrogels are further classified on the basis of physical and chemical stimuli. These materials respond to changes in physical as well as chemical stimuli factors like changes in temperature, variations in electric or magnetic fields etc. Smart hydrogels find applications in controlling the fluid flow in smart bandages as well as manufacturing electrical, biomedical healthcare including various medical and diagnostic pieces of equipments. Fluid is the main constituent of smart bandages so care may be taken out for choosing the techniques for controlling the flow of drugs in microfluidic channels. Controlling the flow rate of drugs in smart bandages is also a wide area of research. Fluid flow rate can be altered by mechanical tools that help in connecting or disconnecting the channels. Mechanical valves are used to obstruct the flow by introducing either microfabricated elements, moving parts, or membranes [6–8].

Hydrogels find applications in targeted drug delivery and tissue engineering due to the ability to prepare the gels of any desired dimensions. Click hydrogels belong to the family of biomaterials that play a major role in controlled drug delivery and protein release [9]. Nanomaterials are the future of medical industry and nano drugs along with nano hydrogels are going to set a revolution in the targeted drug release. The size of nanogel ranges from 1 to 1000 nm. The shape and characteristics of nano drugs are also modified as per the response to the external stimuli. It enhances the therapeutic impact by delivering the drug encapsulated in it to the targeted area or diseased part. The nano gels may help to revolutionize the pharmaceutical market [10–12]. Hydrogels are commonly found in hygiene products such as children's diapers, sanitary pads, and wound dressing materials. Presently, hydrogels are associated with high production cost. The hydrogels used in soft contact lenses make them elastic and comfortable to wear. Coloured lenses can be made by embedding light-reflecting particles along with hydrogels. A variety of application-specific hydrogels have been used in contact lenses. Soft contact lenses besides serving the purpose of correcting eye vision are also used as a source of drug delivery to the eyes [4,13,14]. Another important application of hydrogel is in wound management techniques. Cleanliness of wound is the prime requirement in healing it effectively. Wound is to be kept moist and excess exudate is to be soaked out for better healing. The hydrogels are effective in absorbing the exudate, encapsulating the toxins, and odour present in exudate besides protecting the wound from getting contaminated. The wound may be kept safer by using hydrogels of auto-healing capability. The use of Nano drugs may help in better wound healing by targeting a specific tissue or cell [15,16]. The water-retaining property of hydrogel helps in better oxygen and vapour exchange in the wounds like burns and ulcers. Hydrogels act as a coolant in case of burn victims to relieve the pain. Cavity wounds are also treated with hydrogel dressing materials. Shallow as well as deep open wounds are to be taken care with amorphous hydrogels. The bacterial infection inside the wound hinders the healing process. In such cases, silver and iodine play an effective role in controlling the spread of microorganisms. The hydrogel encapsulating the silver nanoparticles is released at the infection site to counter the spread of infection. The future of smart hydrogel wound bandaging depends upon demand from the public and wound management industry. There is a need for cost-effective smart dressing techniques. Hydrogels have remarkable properties that have popularized their use in drug delivery systems. The density of the crosslinks in the matrix or affinity to water is adjusted to control the porosity characteristics of a hydrogel. The porous structure enables the hydrogel to encapsulate the drugs into it and release later on. Different researchers worldwide are working on smart bandaging where drug release is carried out by controlling the environmental factors. Drug release by diffusion principle involves matrix or reservoir devices. Drug release carried through pores is proportional to square root of time in matrix system contrary to the drug release in reservoir system where it is independent of time. Drugs coated with hydrogels or encapsulated in the hydrogels serve as a means to diffuse the drugs into the targeted area. Hydrogels in plastic surgery present a tissue-friendly approach for burn victims as these lower the risk of infection and inflammation.

A conventional system of drug delivery may cause side effects in certain cases. The hydrogel-based drug delivery system can be made to stop the delivery of drugs as per the environmental stimuli. It may help to counter the side effects in specific cases by blocking the drug release. Hydrogel-based drug delivery system may be a boon for targeted drug delivery in case of deadly diseases. Diabetes is a chronic disease affecting millions of people worldwide. Hydrogels being lightweight, biocompatible may be good to use in diabetic management techniques like delivery of insulin, and wound management of a diabetic patient. Changes in blood sugar concentration may be monitored by hydrogel-based devices with certain restrictions. The use of hydrogels in flexible electronics may unfold the ways for use in future diagnostic techniques for improving the health condition of the patient[(17–21)]. A lot of people in this world are suffering from organ failure due to one reason or the other. It employs the use of bioengineering and life sciences to provide an organic substitute for the regeneration of diseased or fractured parts. Hydrogels are used for space-filling or serve as a carrier to deliver encapsulated bioactive materials to the cells for development of specified tissue or organ.

The hydrogel material may stay in close proximity with the organ tissues or cells without damaging them[(22)]. Accidents or even small cuts in case of some patients lead to uncontrolled bleeding and if not taken care on time may lead to a life threatening condition. The diabetic or cardiac patients are at a high degree of risk. The present techniques of stopping the bleeding are a little risky as it involves an expert hand of physician to put solid plugs at the bleeding site or vessel. In certain cases, multiple plugs are required to be placed at the bleeding site. Traditional methods use bandages or gauzes or sutures to close the bleeding wound. The use of these techniques is fatal for the patient and may cause infection. Hydrogels are the best substitute in modern bandage technology for coagulation. Since hydrogels are being used directly on wounds, it may be confirmed that suitable material is used for fabricating hydrogels. Hydrogels embedded with antibacterial properties may help in soaking the excess exudate as well as in stopping the spread of infection. Hydrogels are the future solution, as they respond to different stimuli conditions and may serve effectively in stopping the bleeding. The hydrogels in the future may be used to simulate the blood vessels that are basic requirement for rebuilding the diseased tissue. Hydrogel serves as a plug to stop the bleeding blood vessels by stuffing the hydrogel in the punctured vessel. The hydrogel on coming in contact with the warm blood swells and seals the vessel. The bleeding is stopped preventing further loss of blood. The swollen hydrogel can be removed by lowering the temperature as it detaches the hydrogel. Hong et al had developed a photo sensitive hydrogel that successfully sealed a bleeding carotid and heart artery of a pig under controlled parameters. Hydrogels embedded with antibacterial agents may help to fight infection in the wounds[(23–27)]. Hydrogels are used to help the patients in providing hot and cold compress. The compress can be designed in desired shapes as hydrogels are foldable in shape.

The literature review reveals that smart bandages require interrupted supply of specific drugs as per the wound requirement. The use of hydrogels in smart bandages may help in controlling the drug supply to the wounds for effective healing. Hydrogels resemble the living tissues due to their softness, high porosity value, and capability to store water contents. pH sensitive hydrogels have been fabricated inside the microchannel to analyse the flow control through microfluidic channels. Kurnia et al presented a computational study for administrating the flow control using stimuli sensitive hydrogels. Kalairaj et al reported thermal sensitive hydrogel for manipulating the flow. Sikdar et al have reported the use of different smart hydrogel materials for a variety of applications. Different types of synthetic hydrogels have been proposed by researchers worldwide but the use of natural hydrogels in smart bandages is yet to be investigated[(6,28–30)] [(31)] A typical smart bandage using the concept of microfluidics is shown in Figure 1**.** The main components of a smart bandage are drug chambers, sensors, microcontroller, sink, and the active area. Drug chambers encapsulate the drugs and drugs are released on receiving the signals from microcontroller. There are hydrogels embedded within the drug chambers that help in the controlled release of drugs. The sink collects the exudate from the wound and may help to soak the exudate and waste fluid. Drugs are supplied to the active area of bandage through microfluidic channels. The sensors placed in the active area of bandage monitor the change in oxygen, moisture, and pH of the wound[(31,32)].

Here, natural and economical (*Plantago ovata*, *Salvia hispanica* L.) hydrogels have been investigated with respect to their abilities to control the drug flow within microfluidic channels in smart bandages. For comparison, one synthetic hydrogel has also been investigated. The hydrogel particles absorb the constituent fluid and obstruct the channel for the flow of the drug for achieving the desired flow rate. Investigations are carried in two parts. In first part, the individual hydrogels are weighed and their weight increase is noted after soaking for a limited time. In the second part, how fast the hydrogels control the drug flow is investigated. A comparison between flow rate of different hydrogels is sought out in the section below.

2 Methodology

The experiment was conducted to analyse the effect of hydrogel on flow rate of drug through the microfluidic channels. The first step in the experimentation was the assembly of drug chambers. Three transparent drug chambers (Figure 2) of radius 2 mm and 4 cm length were made using heat shrink tubes. Glass wool was inserted inside the drug chambers so that the hydrogels

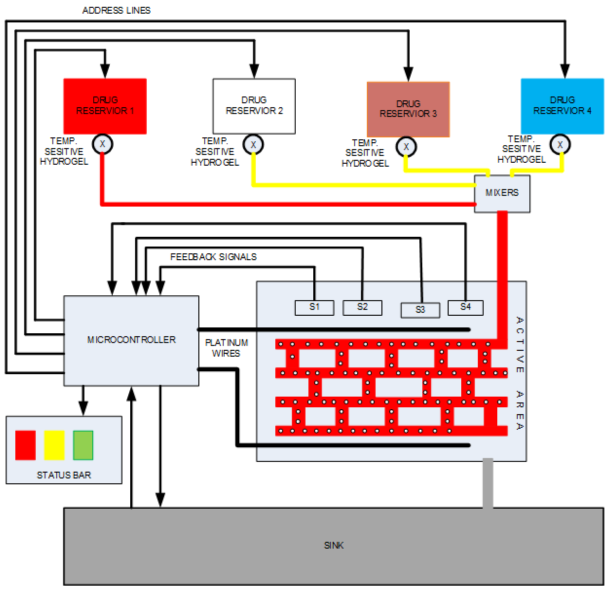

Fig 1. Geometrical outlay of hydrogel based bandage [33].

did not flow with the drugs into the microfluidic channel blocking the passage of drugs. The microfluidic channels fabricated using PDMS may vary in dimensions ranging from 180 -1000 microns. The channels fabricated using PDMS are connected to drug chambers [33]. Three types of hydrogels Synthetic hydrogel, *Plantago ovato*, and *Salvia hispanica* L. were taken for the investigations. All of the hydrogels were taken in the raw form as available in the local market. Natural Hydrogels of quantity 0.150 g and 3 synthetic hydrogels were placed inside the outlets of drug chambers. Sodium chloride, Povidone iodine, H_2O_2 were taken as drugs and the solutions were supplied to the drug chambers through small microfluidic channels. Height of bottles containing different medical solutions was adjusted to attain the desired pressure. For estimating the drug absorption by the hydrogels, the increase in weights of the hydrogel particles was noted by weighing them before and after soaking. The set-up is shown in Figure 3. The outlet of chambers was poured in a dish for measuring on the weighing scale. As the change in flow rate was proportional to the increase in weight of the dish, it was noted with respect to time for all the three hydrogels. For comparison, measurements were also carried out using a drug chamber without containing any hydrogel. Camera was used for recording the flow rate.

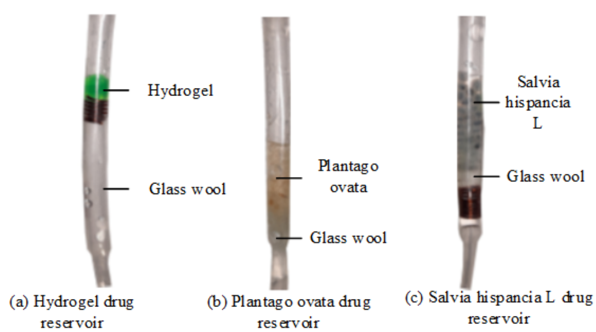

Fig 2. Schematics of drug chamber carrying hydrogel

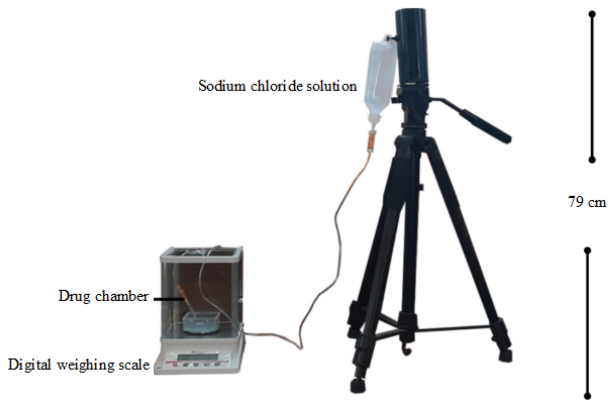

Fig 3. Assembly set up for carrying experimentation

3 Results

As discussed in the methodology for controlling the flow rate inside a microchannel to be used for smart bandages was investigated and fluid absorption capacity of the hydrogels which is the benchmark for studying the flow control mechanism is presented in Tables 1 and 2, Figures 4, 5, 6 and 7. All the three hydrogels show a significant change in volumetric expansion of their size. *Plantago ovato* increases to twice its size within 6 minutes 47 s of keeping immersed in water and whereas *Salvia hispanica* L increases to twice its size within 2 minutes of keeping immersed in water. Synthetic hydrogel increases to twice its size after being kept immersed for 20 minutes. With more absorption of drug w.r.t. time the drug flow is restricted as per the requirement. Hydrogels may be encapsulated inside the drug chambers as per the basic need of the application. The weight of dry synthetic hydrogel taken for the experiment was 10 mg and after soaking in sodium chloride solution, the weight increases to 202 mg within a time span of 43 minutes. The weight of *Salvia hispanica* L. and *Plantago ovato* taken for the experiment was 0.718 g and after soaking in sodium chloride solution of 6.090 g, the weight of Salvia hispanica L. rises to 3.111 g whereas the weight of *Plantago ovato* increases to 6.808 g within a time span of 2 minutes 45 seconds. It may be observed that *Palantago ovato* has fast absorption rate as compared to both the synthetic and *Salvia hispanica* L. hydrogels (Table 1).

Table 1. Weight analysis of hydrogel in sodium chloride solution.

Hydrogel	Dry hydrogel(g)	Swollen hydrogel (g)	Time (s)
Synthetic hydrogel	0.01	0.20	2580
Plantago ovato	0.72	6.81	165
***Salvia hispanica* L.**	0.72	3.11	165

Table 2. Weight analysis of hydrogel in H_20_2, Povidone Iodine and Mustard oil solution.

Solution	Hydrogel	Dry hydrogel(g)	Swollen hydrogel (g)	Time (s)
H_20_2	***Plantago ovato***	0.72	5.665	165
	***Salvia hispanica* L.**	0.72	3.789	165
Povidone Iodine	***Plantago ovato***	0.72	5.896	165
	***Salvia hispanica* L.**	0.72	2.855	165
Mustard Oil	***Plantago ovato***	0.72	No change	165
	***Salvia hispanica* L.**	0.72	No change	165

The drug control analysis of various hydrogels and empty drug chamber is plotted in Figure 4. It provides information regarding the increase in weight of sodium chloride solution w.r.t time. It was investigated that *Plantago ovato* blocks the path of drug faster as compared to *Salvia hispanica* L. Synthetic hydrogel shows a continuous increase in weight as it takes more time to absorb the liquid. Empty tube (without hydrogel) shows a linear increase in weight. The results of the flow rate are plotted in

Figure 5.

Plantago ovato and *Salvia hispanica* L. provided better results and hence were further used for investigating the flow rate with Povidone iodine, H_2O_2, and mustard oil. The *Plantago Ovato* and Salvia hispanica L. seeds were soaked in Povidone iodine, H_2O_2, and mustard oil for 2 minute and 45 seconds. The observations are shown in Table 2. The weight of *Salvia hispanica* L. and *Plantago ovato* was 0.718 g. After soaking in H_2O_2 solution, the weight of *Salvia hispanica* L. rises to 3.789 g whereas the weight of Plantago ovato increases to 5.665 g within a time span of 2 minutes 45 seconds. In Povidone iodine solution, *Plantago ovato* shows a considerable increase of 5.178 g and *Salvia hispanica* L. weight rises to 2.855 g after being soaked in the solution for 165 seconds. No considerable change in weight is observed for mustard oil. The results of drug control analysis for *Plantago ovato* are plotted in Figure 6. *Plantago ovato* shows fast control in Povidone iodine solution as compared to H_2O_2 solution. At 25 s *Plantago ovato* completely blocks the flow in case of Povidone iodine solution whereas the flow is completely blocked at 35 s in case of H_2O_2 solution. A comparison for *Plantago ovato* and *Salvia hispanica* L. is plotted in Figure 7 where it is analysed that *Plantago ovato* shows fast control over *Salvia hispanica* L. Flow rate for *Plantago ovata* is better than synthetic hydrogel and *Salvia hispanica* L. The main feature of *Plantago ovato* is that it forms a jelly after absorbing the liquid and hence may be more useful as a sink for the smart bandage to absorb the exudate or residue. The limitations of the developmental work regarding smart bandages carried out by other researchers are the requirement of complicated mechatronics, bulkiness of the bandages, difficulty in designing user specific bandages, and the non-economic design of the bandage. The present research investigates the use of economical alternatives to develop affordable, easily wearable, and medically viable smart bandage.

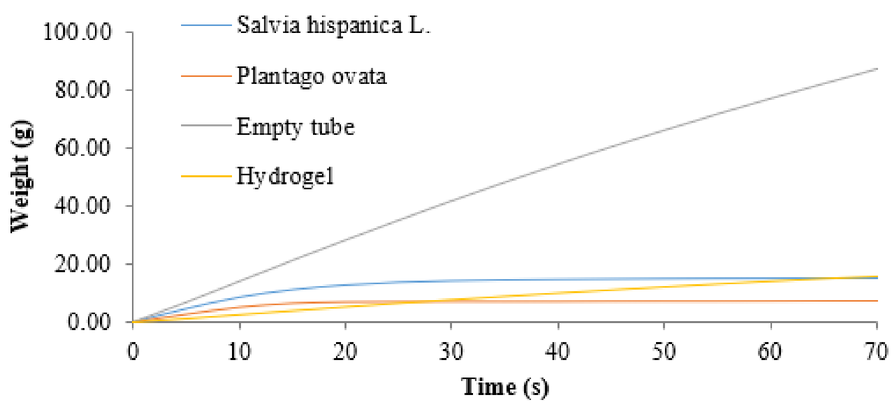

Fig 4. Drug control analysis

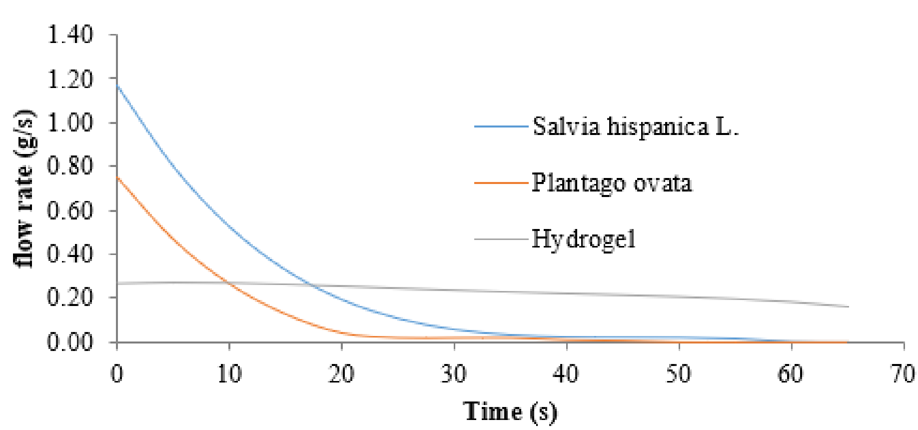

Fig 5. Analysis of flow rate of natural and synthetic hydrogel

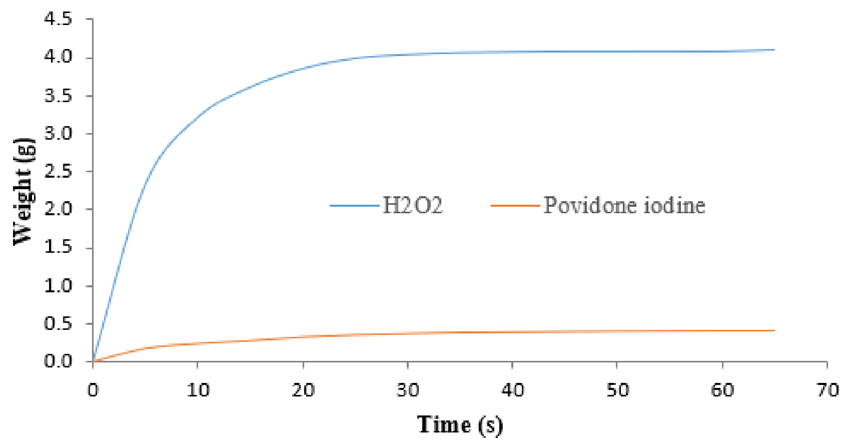

Fig 6. Drug control analysis of *Plantago ovato* in Hydrogen peroxide and providine iodine solution

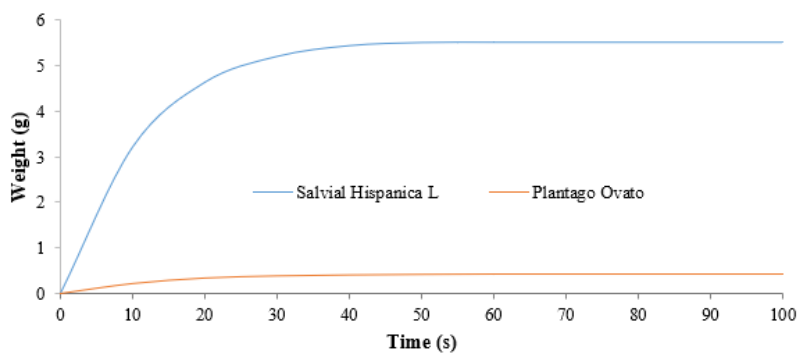

Fig 7. Drug control analysis for *Plantago ovato* and *Salvia hispanica* L. in povidone iodine solution

4 Conclusion

The natural hydrogel from *Salvia hispanica* L. shows a better perspective for automatic controlling the drug flow; whereas, *Plantago ovato* may serve the purpose of absorbing the exudate. Development of a prototype of a smart bandage using *Salvia hispanica* L. for controlling the flow and *Plantago ovato* for absorbing the exudate is in our future plan. The main advantage of *Salvia hispanica* L. and *Plantago ovato* is that the smart bandage will be very economical for the use of masses. The advantage of the proposed bandage is that it uses only the raw natural materials which are easily available in the market and provides satisfactory performance.

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