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Research paper

Effect of Flow Behavior on the Production of PVA/Dextrin Microspheres

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Abstract

This work studies the production of microspheres from biopolymer towards using as drug carrier and elucidation of the effect of flow behavior on the properties of microspheres. Poly(vinyl alcohol) PVA of 2, 2.5, 3 wt% was mixed with 18% Dextrin using sonication process and then stirred for 20 h at 5°C. Different samples were taken after 4, 8, 12, 16, and 20 hr during stirring process for each concentration. Optical Microscopy, Zeta potential and AFM were used to check the size, shape, distribution, and stability of microspheres at rest. Dynamic viscosity and shear stress of the samples were tested under (0.1-50) s^{-1}shear rates at 37°C in vivo condition by using con-plate viscometer**.** The result show that the microspheres were formed in spherical shape in sizes up to 150 micrometers and the increasing of PVA concentration lead to the increasing of wall microsphere thickness**.** The first concentration have incipient instability and moderate stability for the second and third concentrations. Also, the viscosity curve exhibited non-Newtonian flow and shear thinning behavior at 2, 2.5 and 3 wt% PVA/Dextrin emulsion. The microspheres deformed at 50 s^{-1} shear rate for the first concentration. The microspheres keep stable in the second and third concentration due to the gradually shear thinning effect**.** The stability of microspheres of third concentration was higher than others at rest and dynamic test. A good agreement occurs between viscosity behavior and the microspheres characteristics and stability.

Keywords: *Bio-polymer, Flow behavior, Microspheres, Shear thinning, Stability.*

1. Introduction

The use of naturel and synthetic biopolymers is very popular in pharmaceutical industries. This is because they are biocompatible, nontoxic, biodegradable and low costs [1,2]. Biopolymers are used in drug delivery applications in the form of microspheres. To get maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time thereby causing little toxicity and minimal side effects.There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One approach is using microspheres as carriers for drugs [3-5]. Microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, genetic materials, safe and targeted. It is also, effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body [6-9].

Microspheres can be prepared by various techniques, such as solvent evaporation, phase separation (coacervation), spray drying, precipitation, polymer coating, layer by layer and emulsion diffusion. The behaviors of microspheres affected mainly by PH, concentration and viscosity of the polymer used, crystallite, molecular weight, drug type, size and shape of matrix [10-12].

Natural polymers, such as natural gums, and polysaccharides are used in drug delivery system. Starch is one of the polymers that is suitable for production of microspheres. It is non-toxic, biodegradable, and relatively inexpensive material has been used widely in the entrapment of food ingredients, also starch has a long tradition as an excipient in drug formations.

To achieve specific properties, starch modified chemically, physically or enzymatically. Starch is not soluble in water below 80°C and gelatinization temperature is low. This can be a clear disadvantages in some reactions. To overcome this disadvantage, native starch is partially hydrolyzed being modified into several modified starch (Dextrin), which is a water-soluble starch because its molecular weight and viscosity decreases. Acid hydrolysis also affects viscoelastic properties of starch. Acid modified starch show Newtonian behavior. Storage and loss moduli (G`, G``) decrease upon acid hydrolysis. Dextrin is saturated carbohydrate therefore it can resists fungi, while native starch can be attacked by microorganism [13-18].

Poly (vinyl alcohol PVA) used for biomedical applications due its biocompatibility. PVA used as stabilizer and due to its easily degraded, starch-PVA blend used as drug carrier. Also, this blend is more valuable than homo PVA polymer [19-22].

In the present work, dextrin mixed with PVA in different concentrations to produce emulsion containing microspheres, to be used as drug carrier[23].Optical microscopy,atomic force microscope, particle size, cone-plate viscometer and zeta potentialwere used to check the microspheres characterization. The relation between the microspheres behavior and shearing force and viscosity at constant shear rate was analyzed. Also the stability of microspheres with the shear rate change during non-Newtonian flow and shear thinning effect of different emulsion was discussed.

2. Materials and Methods

2.1 Materials

PVA provided from (LOBA Chemie Pvt., Ltd.), Dextrin from maize starch (Hydrolysis starch called dextrin),and sodium bicarbonate from (Merck)comppany. Distilled water used for all samples.

2.2 Preparation of Microspheres

18 g of Dextrin was added to 82 ml of (50mM sodium bicarbonate) to form solutionNo.1(S_1).S_1 was heated in sealed container in a microwave for 2 min. If the solution is not clear indicating fully gelatinized samples, the solution is heated again, then the solution cooled down to 40 °C. Three ratios of PVA (2,2.5 and 3wt %) were prepared by dissolving certain amounts of PVA in appropriate amounts (50mM sodium bicarbonate) at 80˚C for 30 min to form S_2. 3ml of S_1 added drop wise to S_2 , then subject to sonication at 35 Hz for 5 min at 25˚C. The second step cooling the emulsion in ice-bath at 5 ˚C with continues stirring for 20h. For each four hours interval, sample of the resultantsolution was examined by microscope (by two modes). To test stability, daily microscopic checking done for every sample.

3. Characterization of PVA/ Dextrin Microspheres

3.1 Optical Microscopy test:

The morphology of prepared samples were examined under microscope according to ASTM F728-81 by two modsFig (1). The firstmode is done by adding the drops over the glass slidethen placed under the microscope for analysis. This mode give picture with3D. The secondmode including putting the drops between two slides. This mode give picture with 2D. The particles were measured at 40X magnification using1280XEQ-MM300TUSB device.

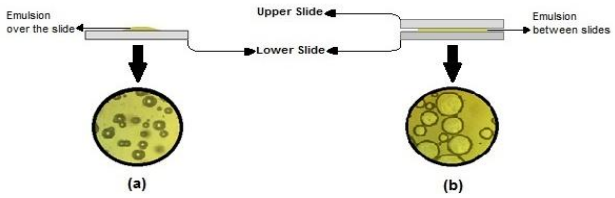


Fig.1: Examining the emulsion using optical microscope according to: (a)first mode, (b) second mode.

3.2 Atomic Force Microscope (AFM) test

The surface morphology of the microspheres was further analyzed using conventional tapping mode of AFM according toASTM E2865.

3.3 Rheological tests

Shear viscosity and shear stress were measured using cone-plate viscometer according to ASTM D7395for different PVA/Dextrin solutions at (0.1-50) s^{-1} shear rate range.

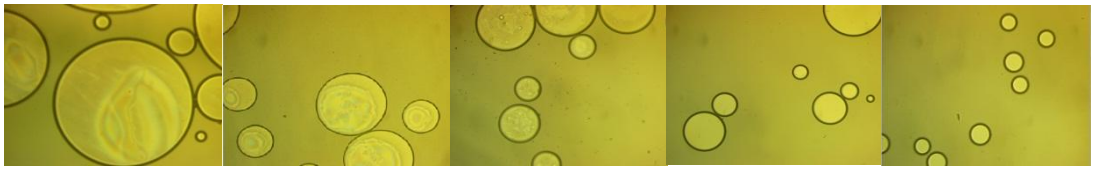
3.4 Zeta potential test

The microspheres stability was tested byusing ZETAPLUS device (Brook haven/USA) according to ASTM E2865.

4. Results and Discussion

4.1 Optical Microscope Result

It is clear from these fig(2-4) that the microspheres were formed in spherical shape in sizes up to 150 micrometers and that the increasing of PVA concentration lead to the increasing of wall microsphere thickness[18] due to the increasing viscosity of emulsion. Also, number of microspheres increased and narrow distribution dominants at higher concentration. The 2.5wt% PVA/ Dextrin solution shows higher number of microspheres with broad distribution. Same behavior obtained in this solution regarding the wall of microsphere-viscosity relation. In the fig (2and4) the microspheres show broad distribution due to the PVA concentration and the viscosity value. The touching between microspheres in these two solutions produce a new microsphere with smaller diameter and higher wall thickness during stirring time increasing. Fig 4 shows that solution of 3wt% PVA/ Dextrin showed relatively higher number and size with lower broadness of microspheres in the same condition. The wall thickness of microspheres were increased due to the chains layers accumulated and viscosity increasing. The diameter of microspheres keep stable in size up to 16h because of stable and strong wall thickness. Shear rate, shear stress and shear viscosity strongly related to the molecular weight, chains morphology and molecular weight distribution of polymer solution. The high shear stress of 2wt% PVA/Dextrin in fig (2,3). The mostly produced small spheres diameters while the larger diameter obtained at 3% PVA/Dextrin where the low shear stress dominated as in fig (4).



a b c d e

Fig. 2: Microspheres behavior of 2%PVA/Dextrin at 5 ℃ after stirring time of (a) 4, (b) 8, (c) 12, (d) 16, and (e) 20hr

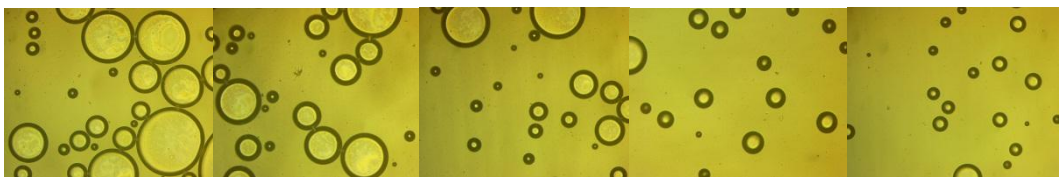


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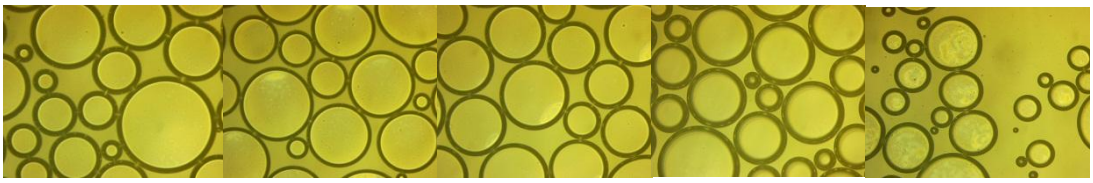
Fig.3: Microspheres behavior of 2.5%PVA/Dextrin at 5 °C after stirring time of (a) 4, (b) 8, (c) 12, (d) 16, and (e) 20hr



a b c d e

Fig.4: Microspheres behavior of 3%PVA/Dextrin at 5 °C after stirring time of (a) 4, b) 8, (c) 12, (d) 16, and (e) 20hr

Diameters of microspheres decrease with time and PVA concentration increased (2 and 2.5wt% PVA/Dextrin) due to the high shear stress and low shear viscosity as fig (5). The diameter of(3wt% PVA/Dextrin) indicate approximately the same size due to the low shear stress and higher shear rate.

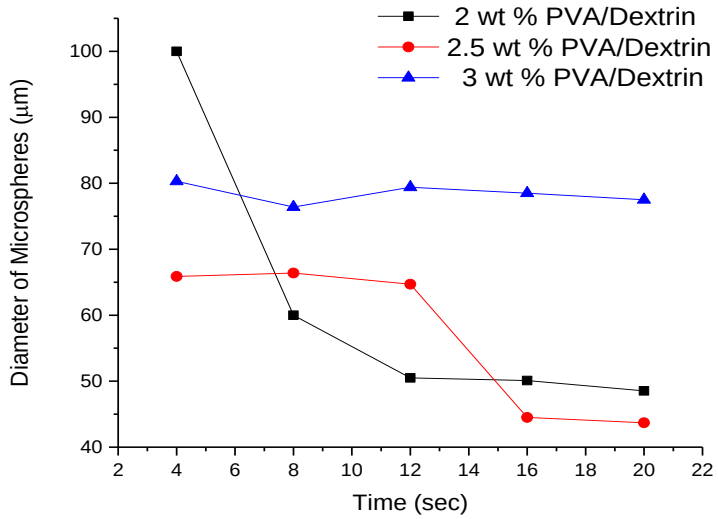
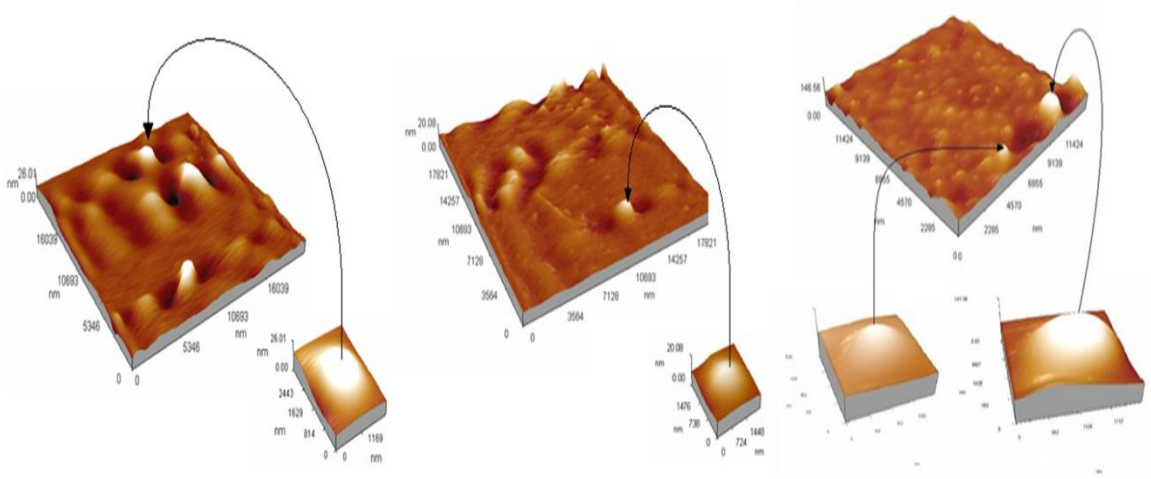


Fig.5: Diameter of microspheres as a function of stirring time at 5˚C of different PVA concentration.

4.2 AFM Results

The microspheres under AFM test indicate different sizes with spherical shape which confirmed with the optical microscopy test. Fig (6) shows 3D microspheres at 20h stirring time for 20x20 µm. The AFM image give more geometrical details about microspheres than that in optical image. Some microspheres in these images were structurally and geometrically completed, while the others must take time or other steps to be completed. There for, higher stirring time and lower cooling temperature must be performed to extend the analyzing and find out the development in the microspheres history grow up. These images were compatible with the previous studies [10 and 13].



(a) (b) (c)

Fig. 6: (a) 3D microsphere image of different PVA/Dextrin emulsions using AFM at (a) 2% PVA (b) 2.5 PVA (c) 3% PVA.

4.3 Rheological Results

Fig(7) shows the relationship of viscosity and shear rate for different PVA aqueous solutions. The non-Newtonian flow behavior was more clear with PVA concentration increasing. The alignment of PVA chains with the velocity gradient increasing produced the shear thinning phenomena. This phenomena increased with the shear viscosity increasing and shear stress decreasing. Therefor shear stress, shear rate and shear viscosity together controlled on the any deformation with PVA structure.

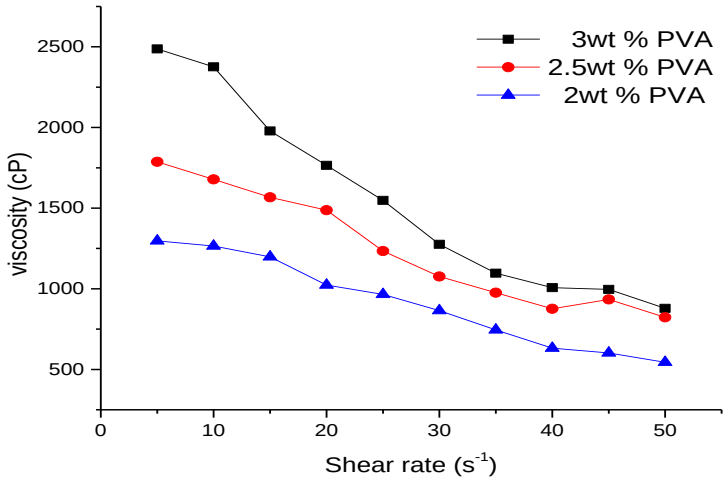


Fig. 7: Viscosity as a function of shear rate for the different PVA aqueous solution.

To simulate the human body conditions, the microsphere prepared in phosphate buffer solution (PBS) and the rheological test carried out in cone-plate viscometer in 37.5°C with (0.1-50)s^{-1} shear rate range, which similar to that presence in veins. Fig(8) shows both viscosity-shear rate relationship and optical images according to the first mode. It is clear that the behavior of all the samples showed reduction in viscosity as shear rate increased. Also, low concentration (2% PVA) firstly the viscosity decreased with shear rate increasing up to 20s^{-1} then viscosity indicates fluctuating with the shear rate. Finally the microspheres were destroyed at higher shear rate. Also, these samples exhibited non- Newtonian flow and shear thinning behavior specially at higher concentration . This is because the PVA chain alignment at higher velocity. The low viscosity through Newtonian flow behavior of 2% PVA was the most parameter effect on the construction of the microspheres and its behavior with the shear increasing at 37 ˚C. This type of PVA/Dextrin solution may be more suitable at low shear or static conditions. In the other side the 2.5% PVA/Dextrin solution exhibits gradually reduction in viscosity up to the 35 s^{-1} and provide the microspheres the ability to survive. The viscosity in the 3% PVA/Dextrin was the highest among these three solutions according to the high PVA concentration. In this case, sever decreasing in viscosity was observedup to 25 s^{-1} due to the change in the structure of PVA and dextrin. The redaction in viscosity means the disentanglement and orientation of PVA and starch chains which represent the major parameter effect on the structure of solution. The changing in polymer chains includes the microspheres walls in the solution. The stability and size of the microspheres depend on the shear viscosity and shear stress. At the end of the shear rate range, the most of the microspheres were deformed. It can be seen that the reduction in viscosity at shear rate up to 25 s^{-1} was increased with the PVA concentration increasing. Therefor the 2.5% PVA/Dextrin solution was more suitable to keep the microspheres stable due to the moderate and slowly changing in viscosity at low shear rate

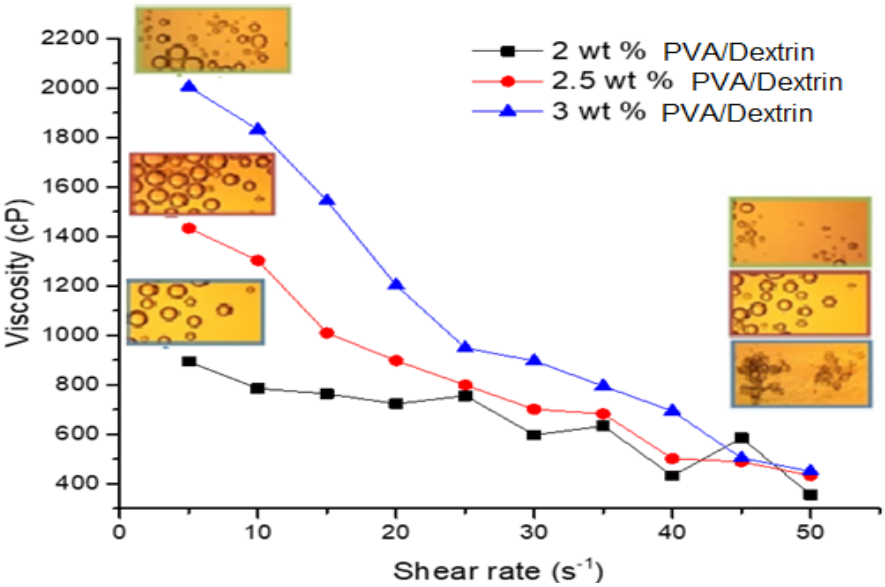


Fig. 8: Microspheres behavior before and after the viscosity's shear rate test for the different PVA/Dextrin aqueous solutions.

The data in fig(9), were confirmed with that in fig (8). The shear stress was increased with the shear rate increasing for all three samples. The microspheres in (3wt% PVA) sample were mostly degraded due to the high shear stress difference along with the shear rate increasing. The lower shear stress difference obtained in 2.5wt% PVA sample gave the ability to the most of the microspheres to resist the shearing force, while the microspheres

in the 2wt% PVA sample mostly deformed due to the low viscosity and fluctuating in the shear rate.

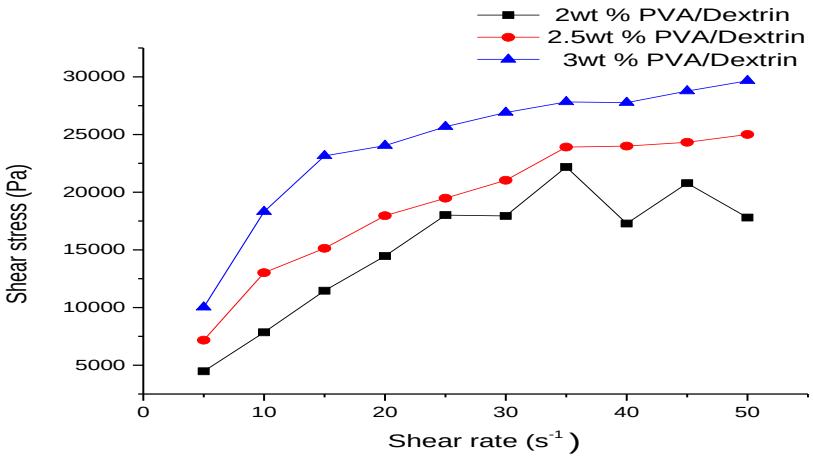


Fig. 9: Shear stress vs shear rate of different PVA/Dextrain aqueous solusions.

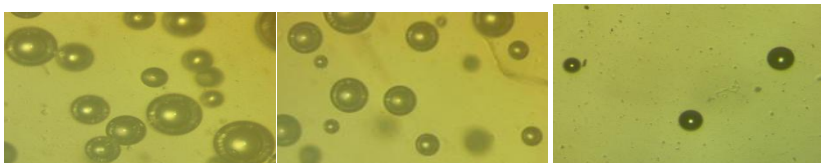
Table 2: viscosity at zero and 50 vs shear and shear stress.

Samples	Zero shear viscosity (η_0)	Shear stress(τ_0) at zero shear viscosity	Shear viscosity (η_{50}) at 50 shear rate	Shear stress (τ_{50})at shear viscosity η_{50}
2%PVA / Dextrin	894	4470	526.5	26325
2.5%PVA / Dextrin	1433	7165	500.02	25001
3%PVA / Dextrin	2004	10020	600.02	30001

4.4 Stability Results

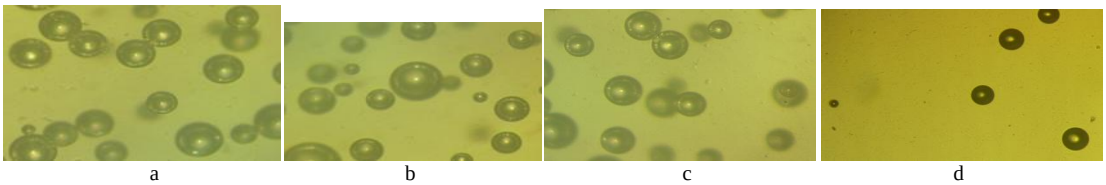
4.4.1 Microscopy

Second mode in optical microscopy was used to check the stability of microspheres of different emulsion samples after20h stirring at 5°C. The number of microspheres relatively decreasing with the number of days increasing for different PVA/Dextrin solutions after 20h stirring time. Fig(10) showed reduction in number of the microspheres after 21 days for 2 wt% PVA/Dextrin solution, while the same behavior of 2.5 wt% PVA/Dextrin occurs after 25 days. This difference in static stability of microspheres number produced due to the difference in viscosity and PVA concentration. Fig (11) indicates different behavior where the number of microspheres keeps., stable with the higher number ofdaysat 3wt% PVA sample because of high viscosity and PVA concentration. The high shear stress and low viscosity of 2 wt% PVA/Dextrin indicate faster degnadation in number of microspheres, which leads to the rapid release pattern.From the other side, the low shear stress and higher viscosity of 3 wt% PVA/Dextrin showed lower microspheres degredation, which may produce slow release pattern in drug delevery applictions as set in fig (12). These result compatible with that of[9].



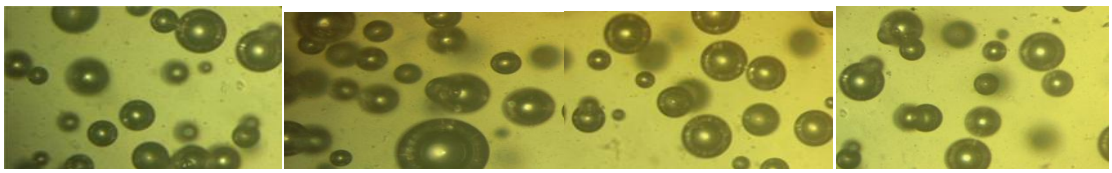
a b c

Fig. 10: The microspheres bahavior of 2 wt% PVA /Dextrinemulsion after 20hr stirring for (a) 7,(b) 14, and (c) 21 days.



a b c d

Fig. 11: The microspheres bahavior of 2.5 wt% PVA /Dextrin emulsion after 20hr stirring for (a) 7, (b) 14, (c) 21, and (d) 25 days.



a b c d

Fig. 12: The microspheres bahavior of 3 wt% PVA /Dextrin emulsion after 20hr stirring for (a) 7, (b) 14, (c) 21, and (d) 31 days.

Fig (13) indicates quantitatively the number of microspher behavior with the number of days in different solution of PVA/Dextren. 3 wt% PVA/Dextren showed high stability with time due to the high PVA concentraion. The number of microspheres were decreased with the number of days for all samples. The number of microspheres of 2 and 2.5 wt% PVA/Dextrin rapid decreases up to 21 and 25 dayesv reprectivelly, while the 3% PVA/Dextrin gradually decreasses up to 31 days, the shear viscosity and shear stress were the most important parameters effect on the stability of microspheres.

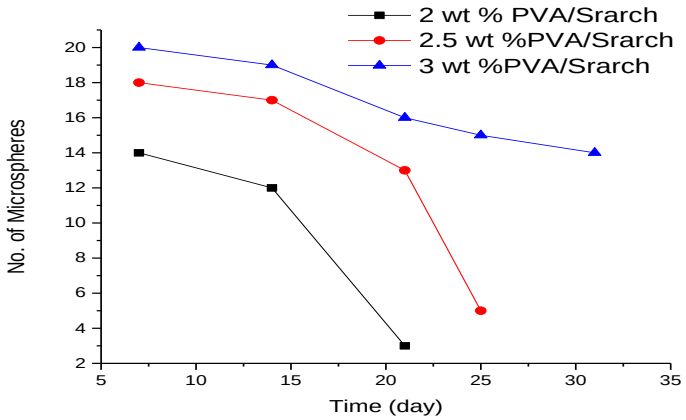
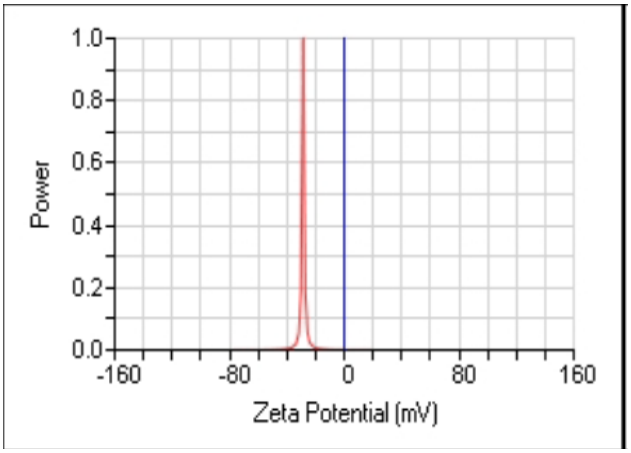


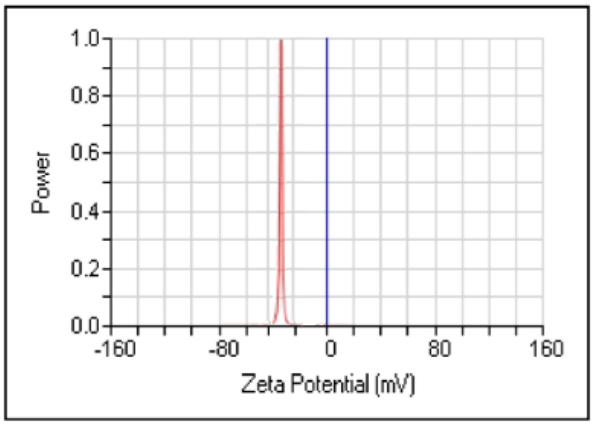
Fig. 13: Stability of microspheres number vs. number of days of different PVA/Dextrin solution.

4.4.2 Zeta Potential

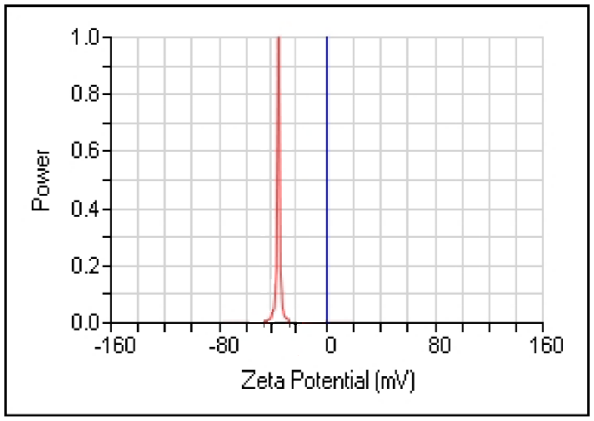
Fig (14) shows zeta potentials for the prepared samples. It is clear that the stability increased with PVA content increased. With 2 wt%PVA , zeta potential value is (-28) mV,wich means that the microspheres have incipient instability. This is due to small amount of repulsion charges available among microspheres. With increasing PVA content, zeta potential increased to (-32) mV and then to (-36) mV, wich indicate that moderate stability occure to increment in repulsion[12,13]. This repulsion will overcome the attractive forces among microspheres and agglomeration will not occure. Zeta potential resultsagree with the stability test by second mode optical image.



(a)



(b)



(c)

Fig. 14: Zeta potential forprepared samples (a) 2 wt% PVA (b) 2.5 wt% PVA (c) 3 wt% PVA

5. Conclusions

1-The microspheres were produced with diameters up to 150 micrometers and diameter keep stable in size with narrow size distribution for the high concentration of PVA. The wall thickness increased with increasing the concentration of PVA.
2-The static stability of low concentration is low and incipient but it is moderate at the higher concentration , The dynamic stability of microspheres with the shear rate increased with the increasing the concentration in vivo conditions. At low PVA concentration showed the deformation of microspheres, while the moderate concentration and high indicates acceptable stability.

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