

FORMULATION AND *IN VITRO* EVALUATION OF METHAZOLAMIDE ELASTIC VESICULAR SYSTEMS

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ABSTRACT

Eye is the most unique organ of the body. Various drug delivery systems are used to deliver drug into the eyes but there are various limitations of conventional systems, so various novel approaches like nanovesicular systems were used to improve ocular contact time, bioavailability, residence time and dosing frequency. Nanovesicular system with elastic properties can provide a controlled delivery of Methazolamide (MZA) which is used to treat glaucoma by inhibiting the action of carbonic anhydrase enzyme. The elastic nanovesicular carriers were formulated using Span 60 (SP 60) with one of the following edge activators (EA): Tween 80 (TW80), Tween 60 (TW 60), Brij 35 (BJ 35), and Brij 58 (BJ 58) in the ratio (90:10; 80:20; 70:30 w: w). The prepared formulae were evaluated for their sizes, entrapment efficiencies (EE %), relative deformability, and *in vitro* release. The results show that the selected formulae (S1, S4, S7, and S8) have the suitable particle size and EE%, thus can be used for any further investigations.

Keywords: elastic vesicles, Methazolamide, Edge Activators, Carbonic anhydrase inhibitors.

INTRODUCTION

Eye contains several protection mechanisms which decrease ocular drug absorption topically and lead to short duration of action. These mechanisms mainly involve the drainage of tear fluid with blinking of the eye leading to about 10-fold reduction in the intraocular concentration of drug (Lang, 1995). Among other reasons which may also cause low drug absorption are the limited corneal permeability and the passage of drug via nasolacrimal duct. Therefore, the ocular bioavailability of topically applied drug solutions is not more than 1-5% (Jarvinen *et al.*, 1995).

To overcome the previously mentioned obstacles which may face ocular drug delivery, several approaches have been used like the vesicular systems (Kaur *et al.*, 2004).

Methazolamide (MZA) is a weakly acidic sulfonamide derivative which is slightly soluble in water. It is indicated for the treatment of glaucoma by inhibiting the action of carbonic anhydrase enzyme. However, MZA was found to have some serious side effects when taken orally such as allergic reactions (e.g. difficulty of breathing, swollen lips, tongue or face), bleeding, and tremors in the hands or feet. Therefore, the topical administration of MZA to the eye is more preferred in order to reduce these side effects. However, the poor aqueous solubility of MZA (~1.7mg/ml at 25°C) (Maren *et al.*, 1977), as well as its low corneal permeability (1.75×10^{-4} cm /hour) (Edelhauser and Maren, 1988) make its topical delivery inefficient. Different techniques have been utilized to formulate MZA in a form that can be delivered topically e.g. cyclodextrin eye drops (Fridriksdóttir *et al.*, 1997), calcium phosphate nanoparticles (Chen *et al.*, 2010), in situ- gels (Qian *et al.*, 2010), cationic nanostructured heterolipid matrices (Youshia *et*

al., 2012) , solid lipid nanoparticles which was prepared by modified emulsion-solvent evaporation (Li *et al.*, 2011).

Moreover, elastic vesicular systems that consist of a mixture of span60 together with different edge activators, can be used to increase the drug residence time and consequently its ocular bioavailability (Kakkar and Kaur, 2011).

The aim of the work in this paper was to prepare and characterize Methazolamide loaded elastic vesicular system.

EXPERIMENTAL

Materials

Methazolamide (MZA) was purchased from Jiaying Taixing chemical and Pharma Co, ltd (Jiaying, China). Brij 35, Brij 58, Span 60, Tween 60, and Tween 80 were purchased from Sigma Chemical Co., St. Louis, USA. Disodium hydrogen Phosphate, ethanol 99% pure absolute, potassium dihydrogen phosphate, and sodium chloride were purchased from Adwic, El-Nasr pharmaceutical CO. (Cairo, Egypt). Spectra/Por dialysis membrane, 12,000–14,000 molecular weight cut off was purchased from Spectrum Laboratories Inc., Rancho Dominguez, Canada.

Equipment

Centrifuge (Herml, Z 216MK centrifug, Gosheim,Germany), particle size analyzer NanoZS (Malvern instruments, Malvern, UK), Rotary evaporator (Janke and Kunkel, IKA Laboratories, Germany), USP dissolution apparatus (Pharma test, Hainburg, Germany), and UV- Visible spectrophotometer (model UV -1601pc; shimadzu, Kyoto, Japan)

Methodology

1- Preparation of MZA-loaded elastic vesicular system

Elastic vesicular system containing Span 60 and edge activators (EAs) (namely Brij 35, Brij 58, Tween 60, and Tween 80) were prepared by ethanol injection method using different weight ratios of Span60: EA (90:10; 80:20; 70:30 w: w). Briefly, Span 60 and calculated amount of MZA were dissolved in 4 ml of ethanol to produce final concentration of 0.05 % (w/v), and then injected into magnetically stirred aqueous solution of the EA (Kakkar and Kaur, 2011). The ethanol was evaporated by Rotary evaporator, and the formed milky vesicular dispersions were used for further investigations.

2- Determination of MZA entrapment efficiency (EE %) in elastic vesicular system

The EE% of MZA in elastic vesicular system was determined by measuring the concentration of free drug in the vesicular dispersion. The non-encapsulated MZA was separated by centrifugation using Nanosep[®]. A definite volume of the prepared elastic vesicular system was transferred to the upper chamber of the Nanosep[®], elastic vesicular system solutions were centrifuged at 5000 rpm at 4°C for 15 minute. The amount of free drug in the filtrate was determined spectrophotometrically at 290nm using a UV- Visible spectrophotometer.

The EE% was calculated according to the following equation as follows:

$$EE\% = \left[\frac{W_t - W_f}{W_t} \right] \times 100 \quad (1)$$

Where W_t is the total amount of drug used in the formulation and W_f is the amount of free drug remaining in the supernatant.

3- Particle size (PS) and zeta potential (ZP) analysis of elastic vesicular system

The PS and ZP of elastic vesicular system were determined at 25°C using particle size analyzer NanoZS (Guinedi *et al.*, 2005). Size and charge measurement using this device is based on Dynamic Light Scattering (DLS). Samples were transferred to disposable polystyrene cells or disposable plain folded capillary zeta cells, and all measurements were performed in triplicate.

4- Measurement of elasticity of the vesicles (Relative deformability)

The measurement of elasticity (Relative deformability) of the elastic vesicular system loaded with MZA solution was carried out by extrusion technique (Van den Bergh *et al.*, 1999, 2001; El Zaafarany *et al.*, 2010) through a locally fabricated stainless steel pressure filter holder. The vesicles were extruded through membrane filters with pore size of 220 nm at constant pressure of 0.248 Bar. The experiments were carried out in triplicates and relative deformability as an indicator for elasticity was calculated according to the following equation (Salama *et al.*, 2012):-

$$D = \frac{j}{t} \left(\frac{rv}{rp} \right)^2 \quad (2)$$

Where D is the deformability index (ml/s); j is the amount of suspension which is extruded (ml); t is the time of extrusion (s); rv is the size of vesicles after extrusion (nm); and rp is the pore size of the barrier (nm).

5- *In vitro* release of MZA from elastic vesicular system

In vitro drug release was done by dialysis membrane diffusion technique using USP dissolution apparatus fitted with glass cylinder (10cm in length and 2.5 cm in diameter). The cylinders were fixed in the device shaft from one end using clips while the other end was covered by cellulose membrane (Spectra/Por dialysis membrane 12, 000–14,000 molecular weight cut off) to retain elastic vesicular system while allowing the free drug to be released into the dissolution medium in the vessels (Nasr *et al.*, 2008; Hathout *et al.*, 2007). Accurately measured amounts of elastic MZA vesicular system equivalent to 1mg MZA were transferred to the glass cylinder, and the cylinder was immersed in 50 ml dissolution media phosphate-buffered saline (PBS) adjusted at PH (7.4) for Methazolamide elastic vesicular system (Attama *et al.*, 2008).

The dissolution media was kept at 37°C ± 0.5 while the cylinders were rotated at 50rpm. 1ml samples were withdrawn at different time intervals (0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8 hours) and replaced with 1ml of fresh medium, then assayed spectrophotometrically at 290nm. All the results presented in the release studies are the mean values of three runs.

6- Determination of drug release kinetics

To know the mechanism of drug release from the selected formulae, the data were treated according to first-order (log cumulative percentage of drug remaining vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time), zero order (cumulative amount of drug released vs. time) pattern, and Korsmeyer-Peppas model (plotted as log cumulative percentage drug release vs. log time) (Dash, *et al.*, 2010; Prabhu, *et al.*, 2010).

7- Physical stability studies

A- Determination of the percent of retained MZA in elastic vesicles after storage

The stability study was carried out by investigation the ability of the selected elastic vesicles formulae (S1, S4, S7, and S8) to retain the drug (drug retention

behavior). The elastic vesicles formulation was kept at refrigeration temperature (4-8°C), throughout the study, elastic vesicles formulations were stored in sealed glass vials. The samples were withdrawn at different time intervals zero time, after three month, and six month. The drug leakage from the formulations was analyzed spectrophotometrically as previously described in section (2) (**Patidar and Jain 2012; Shahiwala and Misra 2002**).

B- Vesicle size analysis

Aggregation or fusion of the vesicles as a function of time was determined by measuring the changes in vesicles diameters for the selected elastic vesicles formulae (S1, S4, S7, and S8), after stored in sealed glass vials at temperature (4-8°C), at time intervals zero time, after three month, and six month using (DLS) technique as previously mentioned in section (3) (**Patidar and Jain 2012**).

RESULTS AND DISCUSSION

Nanovesicular elastic systems were prepared using ethanol injection method. Different ratios of Span 60 to edge activators were tested in order to choose the formulae which show the highest encapsulation efficiency along with small size to be used for further investigations. Data shown in Table (1) reveals that the percentage of MZA entrapped in the prepared elastic vesicular systems were in the range of 23 to 94%.

Generally, all tested formulae (S1-S12) showed high EE% values. The high values for EE% could be due to the high transition temperature (T_c) of Span 60. It was previously reported that Span 60 showed high EE% compared to the unsaturated Span 80 when tested for the entrapment of various drugs (**Yoshioka et al., 1994; Lingan MA et al., 2011; Abdallah et al., 2013; Akhilesh et al., 2012**).

Statistical analysis showed the effect of Span 60: EA ratio on EE%, since the difference between formulae S1, and S2 was not significant. However, when edge activator (EA) content increased to 30%, the EE% decreased to 68.36%. While for formulae S4, S5, S6, S7, S8 and S9 there were no significant difference between the EE% values, when the content of EA was 10, 20, and 30%. However, for S10, S11, and S12 which contained Brij 58, we observed significant decrease in EE% with the increase in EA content ($P < 0.05$).

It was previously found that the increase in the content of EA result in pore-formation of vesicular bilayer until the concentration reaches a certain threshold. When, such threshold is reached vesicles based on micelles or mixed micelles start to form, leading to a decrease in EE% (**Van den Bergh et al., 2001**).

All formulations in Table 1 show a mean Particle size (PS) less than 1 μ m in diameter. As we screened the size of different formulae we observed that S1, S4, S7, and S8 showed the smallest size and high drug entrapment values when compared to other vesicular formulations. The size of S1, S4, S7, and S8 ranged from 270 to 329 nm; hence they were selected for further investigations.

Generally, the use of edge activators with lower HLB resulted in vesicles with smaller size (**Yoshioka et al., 1994; Basha et al., 2013**). The relationship observed between vesicle size and surfactant HLB could be due to the decrease in surface energy of vesicles, prepared by these surfactants. Vesicles prepared using low HLB surfactants are previously reported to have smaller size compared to those prepared by high HLB surfactants (**El Zaafarany et al., 2010; Akhilesh et al., 2012**).

Thus, upon comparing the PS of formulae (S1, S4, S7, and S8), we found that the smallest PS was for S1 composed of Span 60 and Tween 60. The variation in PS noticed between different formulae can be explained by the difference in HLB values of their EAs components. The HLB values for different EAs are 14.9, 15, and 16.9 for TW60, TW80, and Brij 35 respectively. Among the different EAs; TW60 showed the lowest HLB value and smallest PS when measured by (DLS).

For Brij 35 (formulae S7 and S8) as EA, it was noticed that by increasing the ratio of EA from 10 to 20 % the PS of vesicles decreased from 315.53 to 279.133 nm.

The zeta potential (ZP) values of all prepared elastic vesicular system were in negative region ranging from -12.86 to -30.66mV. The negative charge on the surface of elastic vesicular system is responsible for forming a shield that prevent vesicles from aggregation and impart colloidal stability (Wilson *et al.*, 2008; Huang *et al.*, 2011). The recorded values for Tween 80 elastic vesicular system were formed to be near the values recorded by (Basha *et al.*, 2013) which was in the range from -23 to -29 mV for vesicles of similar components to those in our study.

Elasticity is an important character of elastic vesicular formulations, which can squeeze to pass through pores of biological membranes and decrease the risk of vesicle disrupted while passing through membrane (El Zaafarany *et al.*, 2010). This property differentiates elastic vesicles from other vesicular systems.

The elasticity can be expressed by relative deformability. Fig 1 reveals the average deformability of formulae (S1, S4, and S8). It demonstrates that all formulae have elastic characters. A special properties for Tween 80 is highly flexible and non bulky hydrocarbon chains (El Zaafarany *et al.*, 2010). in addition to the unsaturated alkyl chain (double bond) which render vesicles prepared using Tween 80 more membrane permeable (Abdallah *et al.*, 2013).

Fig 2 shows the *in vitro* drug release profile of MZA solution, and selected formulae (S1, S4, S7 and S8). It was observed that MZA solution released approximately 100% of drug within 4 hrs, it was significantly higher than all tested elastic formulae ($P < 0.05$). Elastic vesicular formulations S1, S4, S7 and S8 showed 90.31 %, 97.64%, 77.22 % and 95.53% drug release respectively in 8 hrs. The result of *in vitro* drug release profile of the formulations showed that elastic vesicular formulations provides more prolonged release of MZA when compared to MZA solution.

Table 2 shows that formulae S4, and S7 followed zero order release kinetics. This indicated that the drug release was independent of concentration of drug entrapped (Prabhu, *et al.*, 2010). However the elastic vesicles S1, and S8 released MZA by diffusion controlled mechanism. This may be due to the formation of a core enriched with active compound leading to a membrane release governed by Fick's law of diffusion (Muller, *et al.*, 2002). The difference between S7, and S8 in the kinetic of release can be due to the increase in EA content which leads to the increase in the tendency of pore-formation in vesicle bilayers and hence their permeability of MZA from vesicles lead to the change in release mechanism (Basha, *et al.*, 2010). The value of n characterizes the release mechanism of drug as described in Table 2. They were higher than 0.89 for all formulae which indicate that the systems follow Super case II mechanism (Dash, *et al.*, 2010).

The stability results for MZA retained in elastic vesicles formulae (S1, S4, S7, and S8) after 180 days, are demonstrated in Fig 3. Statistical analysis shows that there is a significant difference between the values of EE% for freshly prepared vesicles and after storing the vesicles for a period of 90 and 180 days for all tested formulae except S7 which didn't show any significant difference after a period of 90 days ($P < 0.05$).

The effect of storage on the mean particle size of elastic vesicles formulae (S1, S4, S7, and S8) is demonstrated in Fig 4. The results showed significant increase in the particle size of the stored formulae after periods 90 and 180 days, with exception of S8 which didn't show any significant change in size when measured after period of 90 days ($P < 0.05$). These results may be due to the fusion and aggregation of the vesicles after storage (**Padamwar and pokharkar 2006**).

Table 1. The composition of different elastic vesicular system loaded with MZA preparations, Entrapment Efficiency, Particle size and Zeta potential (mean \pm SD)

Zeta potential (mV) \pm SD	Mean Particle size (nm) \pm SD	Entrapment Efficiency Percent EE% \pm SD	Weight Ratio	Formulae Composition	Formulae Code
-16.3 \pm 0.7	276.26 \pm 2.77	82.80 \pm 0.65	90:10	Sp60 + Tw60	S1
-15.6 \pm 1.53	704.93 \pm 8.64	81.99 \pm 0.18	80:20	Sp60 \pm Tw60	S2
-14.76 \pm 1.07	585.1 \pm 4.46	68.36 \pm 0.24	70:30	Sp60 + Tw60	S3
-27.7 \pm 1.15	328.56 \pm 3.19	81.74 \pm 0.43	90:10	Sp60 + Tw80	S4
-24.93 \pm 0.51	761.06 \pm 6.15	80.89 \pm 2.20	80:20	Sp60 + Tw80	S5
-30.66 \pm 0.49	657.53 \pm 6.40	78.69 \pm 2.32	70:30	Sp60 + Tw80	S6
-19.73 \pm 0.37	315.53 \pm 1.56	94.19 \pm 0.13	90:10	Sp60 + BJ35	S7
-23.03 \pm 0.68	279.13 \pm 2.45	93.69 \pm 0.15	80:20	Sp60 + BJ35	S8
-14 \pm 0.45	995.66 \pm 3.05	91.94 \pm 0.16	70:30	Sp60 + BJ35	S9
-19.43 \pm 0.51	630.46 \pm 7.59	68.76 \pm 0.26	90:10	Sp60 + BJ58	S10
-21.33 \pm 1.52	531.63 \pm 3.09	27.76 \pm 0.04	80:20	Sp60 + BJ58	S11
-12.86 \pm 0.77	533.46 \pm 8.30	23.29 \pm 1.95	70:30	Sp60 + BJ58	S12

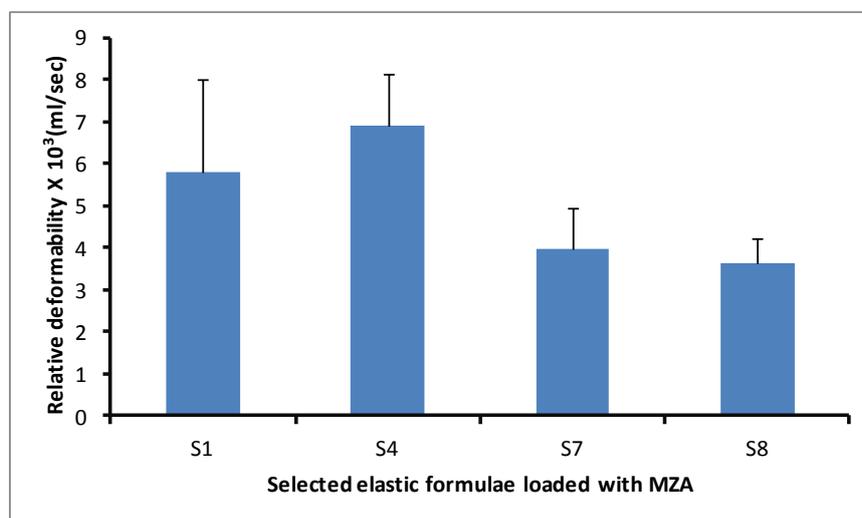


Fig 1: Average of relative deformability (ml/ sec) *10³ of elastic vesicular system loaded with MZA

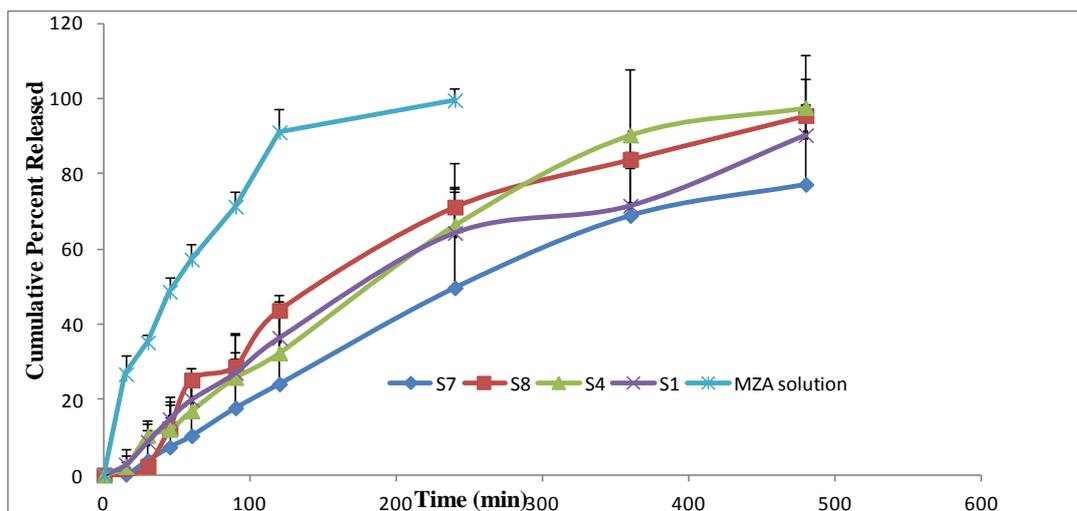


Fig 2: Release profiles of MZA from elastic vesicles solution in PBS at 37°C

Table 2. Kinetic parameter of the release data of MZA from elastic vesicles

Order of release	Peppas model (n)	r ²			Formulae Code
		Higuchi model	First order	Zero order	
Diffusion	1.104	0.992	0.443	0.989	S1
Zero order	1.140	0.988	0.678	0.992	S4
Zero order	1.148	0.985	0.234	0.994	S7
Diffusion	1.484	0.989	0.601	0.982	S8

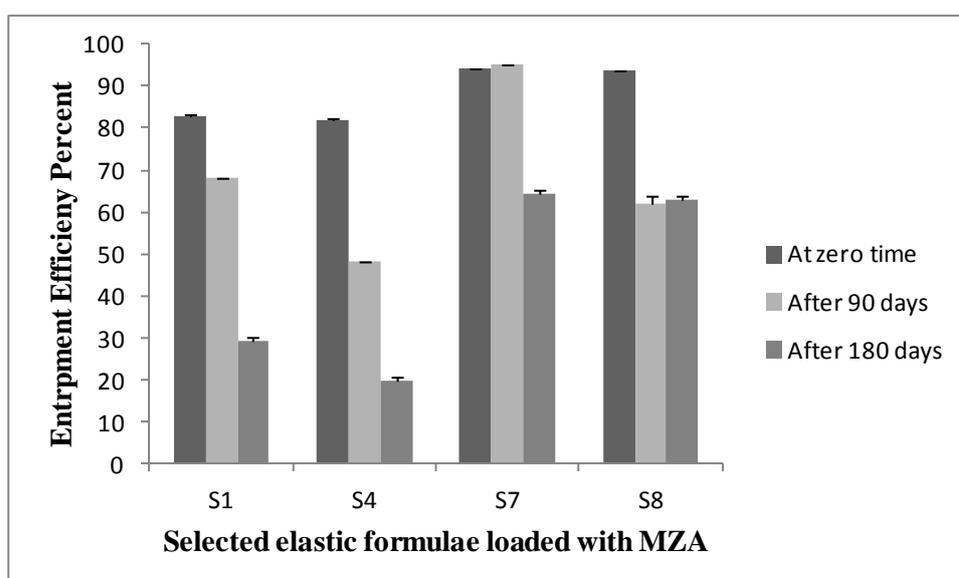


Fig 3: Percent MZA retained in elastic vesicles after interval of time at 4°C

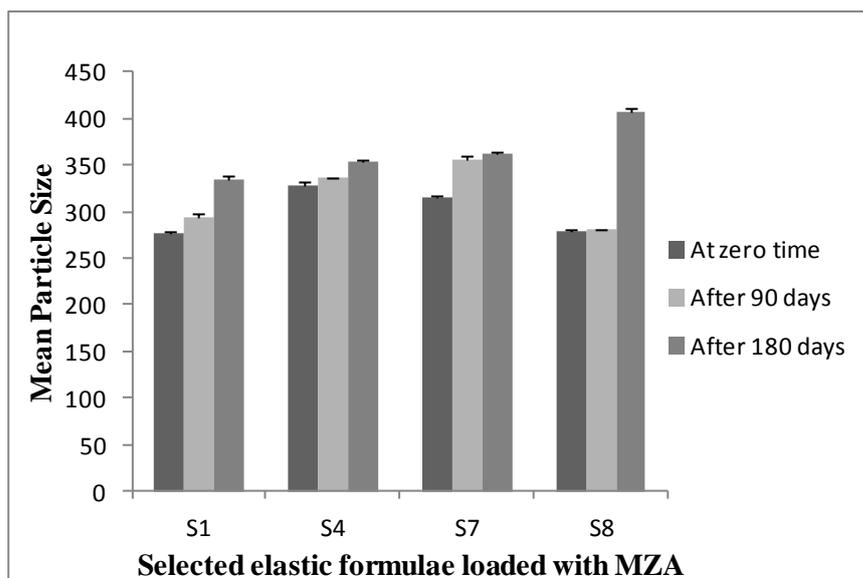


Fig 4: Mean PS of elastic vesicles after interval of time at 4°C

CONCLUSION

MZA was encapsulated successfully in elastic vesicles prepared by mixing different ratios of Span 60: edge activators. The best formulae that have smallest PS, and highest EE %, were selected for further investigations. The formulae showed delayed drug release when compared with drug solution.

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الصياغة والتقييم المعملّي لأنظمه الحويصليّة المرنة المحتوية علي عقار الميثازولاميد

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تعتبر العين من الأعضاء الفريده في جسم الإنسان، وهناك العديد من الأنظمة التي تستخدم لتوصيل الدواء إلي العين، ومع ذلك فإنها توصل الدواء بشكل محدود الي العين وخصوصا الأنظمة التقليديه. وقد وجد أنه من الاتجاهات الحديثه إستخدام الأنظمة الحويصليه النانويه التي من شأنها تحسين وقت بقاء الدواء في العين، وإطالة مفعوله، وتقليل الجرعات المستخدمه منه .

كذلك فإن الأنظمة الحويصليه التي تتمتع بخاصيه المرونه بإمكانها تحسين توزيع عقار الميثازولاميد أثناء إستخدامه في علاج الجلوكوما (إرتفاع ضغط العين).

في هذه الدراسه تم تحضير الأنظمة الحويصليه المتكونه من سبان 60 وعوامل الفاعليه السطحيه وهي توين 60، توين 80، بريج 35، وبريج 58 بنسب وزنيه متعدده (10:90، 20:80، 30:70 وزن: وزن) . وقد تم تقييم الأنظمة المحضره عن طريق قياس متوسط حجم الحبيبات، ونسب كفاءة حوصلة الدواء، وخاصية المرونه وكذلك معدل إنطلاق الدواء من الحويصليات. وقد أظهرت النتائج أن الصياغات المختاره (S1، S4، S7، S8) لديها أحسن متوسط حجم الحبيبات، ونسب كفاءة حوصلة الدواء لذا فإنه من الممكن إستخدامها في الدراسات اللاحقه.