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Preparation and characterization of solid lipid nanoparticles
II. Effect of viscosity, method of preparation and homogenization speed on Physical Characteristics of Solid Lipid Nanoparticles

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ABSTRACT

The objective of this study was to determine the best conditions to formulate solid lipid Nanoparticles using Glyceryl monostearate as lipid matrix which has advantage to be biocompatible and easily degraded in vivo. Different formulation factors were studied including effect of viscosity, method of manufacture and homogenization speed. It was found that method of emulsion solvent injection technique produced smaller particles size than that of the hot homogenization technique for both Tween 20 and Tween 80. The effect of viscosity was prominent with high viscosity value obtained through use of 50 % glycerol as viscosity enhancer. According to homogenization speed, it was found that increasing homogenization speed from 6,000 rpm to 12,000 rpm produced smaller solid lipid nanoparticles with small polydispersity index and homogenous distribution of particle size distribution.

Key words: solid lipid nanoparticles, SLN, high shear homogenization, homogenization speed, emulsion solvent injection, Glyceryl monostearate.

INTRODUCTION

Solid lipids Nanoparticles (SLN) are an alternative carrier system to polymer Nanoparticles or liposomes. They consist of Physiological and biocompatible lipids. It has been claimed that SLN combine the advantages and avoid the disadvantages of other colloidal carriers [1].

Different drugs were successfully prepared as SLN like cyclosporine using high pressure homogenization technique with optimum size of Nanoparticles. Most SLN dispersions produced by high pressure homogenization are characterized by an average particle size below 500 nm and low microparticles content [2].

High shear homogenization utilizes a rotor-stator homogenizer. Rotor-stator homogenizers were developed to increase shear forces while keeping power consumption to a reasonable level [3]. Dispersions produced on the other hand suffer from presence of microparticles, and metal contamination may also be present. Higher homogenization speeds reduced the polydispersity, but did not significantly reduce particle size [4]. Progesterone solid lipid Nanoparticles were prepared using melt – emulsification technique with help of mechanical stirrer and monostearin lipid as solid lipid material and tested the effect of mechanical stirring on drug loading capacity and encapsulation efficiency. Also, drug release was examined [5].

Other methods of preparation of solid lipid Nanoparticles include modified emulsion solvent diffusion or evaporation techniques. The emulsification solvent diffusion method used for preparation of polymer Nanoparticles employing biodegradable polymers like poly (lactic- co glycolic acid) [6].

The aim of this work is to study the influence of method of preparation on the physical properties of solid lipid nanoparticles. Besides, the effect of viscosity and homogenization speed on the physical properties of solid lipid nanoparticles will be studied.

EXPERIMENTAL

Materials

Glyceryl monostearate-technical self-emulsifying (BDH Chemicals Ltd Poole-England). Tween 80 (polysorbate 80), Tween 20 (polysorbate 20), ICI Americas (Wilmington, DE, USA), lecithin, (Spectrum Chemicals & Laboratory Products New Brunswick, NJ). Isopropanol and glycerol and all other chemicals were of reagent grade and used without further purification.

Methods

1. Preparation of solid lipid nanoparticles:

Solid lipid nanoparticles were prepared by several techniques using various ratios of Glyceryl monostearate as lipid phase, Tween 80 or Tween 20 as surfactant and lecithin as co-surfactant. Firstly, the lipid was melted (60-70^0) and dispersed in hot aqueous solution with different surfactant concentrations (0.5, 1, 5 % w/w) and 1% w/w lecithin at the same temperature, by high –speed stirring, using an Ultra-Turrax homogenizer (Ultra- Turrax T – 25, IKA, Germany) at 6,000 and 12,000 rpm for 10 minutes, with 30 seconds intervals every two minutes [7]. The obtained pre-emulsion

were cooled to room temperature (25°C) and their particle size was measured. Also, SLNs were prepared by a modified emulsion solvent injection technique [8], in which Glyceryl monostearate was dissolved in water –miscible solvent (isopropanol) and then rapidly injected into a stirred (approx. 6,000 rpm and 12,000 rpm) hot aqueous phase with surfactant and co-surfactant [9]. The resulting dispersion was then cooled and each sample was diluted with water before measurement and particle size was measured using dynamic laser light scattering apparatus at 25°C. (Mastersizer 2000 vers. 5.54, hydro 2000 S, Malvern instruments Ltd., Malvern, Worcs, UK). Each measurement was performed in triplicate and the particle average diameter and polydispersity index (PI) were determined.

2.2.2. Viscosity measurement:

The viscosity of the aqueous surfactant and co-surfactant phase used in hot homogenization technique was varied by the addition of 10, 30, 50 % w/w glycerol and determined using Brookfield viscometer (Model DV-II+ viscometer, BROOKFIELDENGLABSINC.STOUGHTON, MA.02072U.S.A), at room temperature 25°C.

RESULTS AND DISCUSSION

3.1. Effect of preparation method

Tables (1-12) showed that upon comparing particle size of formed nanoparticles and microparticles that method of emulsion solvent injection technique produced smaller particles size than that of the hot homogenization technique for both Tween 20 and Tween 80. These results were appeared more significantly for particle size of 229±35 nm with 5 % w/w Tween 20 and 10 %w/w GMS, and 354±39 nm with 5 % w/w Tween 80 and 10 % w/v GMS as examples.

However, It was found that the mean particle size depends on the concentration of lipid in the organic water miscible solvent that is not achievable by melt emulsification of similar composition. Very small particles can not be achieved with low lipid loads, while high lipid content will increase viscosity of dispersed phase that hinders homogenization. The results obtained are consistent with those obtained by Menhert *et al* [7] but not in agreement with Schwarz *et al* [10].

Table (1): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 0.5 % Tween 20 using hot homogenization technique and emulsion solvent injection technique at 6,000 rpm.

GMS % w/w	Tween 20 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	0.5	4110±18	4051±21
2		3801±23	3376±56
3		3680±76	3084±77
4		3571±80	2944±6
5		3503±126	2862±7
6		3361±24	2862±110
7		3080±83	2528±5
8		3060±5	2467±0.5
9		2951±8	1794±41
10		2612±85	1458±18

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Table (2): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 1.0 % Tween 20 using hot homogenization technique and emulsion solvent injection technique at 6,000 rpm.

GMS % w/w	Tween 20 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	1.0	3974±14	3438±43
2		3700±24	3169±12
3		3685±7	3037±68
4		3426±2	2797±6
5		3368±23	2166±21
6		3071±161	1855±38
7		3027±2	1382±88
8		2683±39	1257±23
9		2658±43	1142±79
10		2341±23	357±52

Table (3): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 5.0 % Tween 20 using hot homogenization technique and emulsion solvent injection technique at 6,000 rpm.

GMS % w/w	Tween 20 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	5.0	3802±23	3212±68
2		3440±126	3033±20
3		3361±18	2931±15
4		3194±48	2541±7
5		2887±43	2055±0.5
6		2787±42	1643±428
7		2764±6	1211±9
8		2612±88	1011±15
9		2366±11	1008±26
10		2293±369	229±35

Table (4): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 0.5 % Tween 20 using hot homogenization technique and emulsion solvent injection technique at 12,000 rpm.

GMS % w/w	Tween 20 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	0.5	2902±11	2838±32
2		2603±49	1894±6
3		2342±35	1835±7
4		2204±49	1198±6
5		2078±190	915±19
6		1880±25	867±23
7		1849±102	403±3
8		1755±21	325±4
9		989±67	306±6
10		461±102	265±9

Table (5): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 1.0 % Tween 20 using hot homogenization technique and emulsion solvent injection technique at 12,000 rpm.

GMS % w/w	Tween 20 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)±S.D(emulsion solvent injection)
1	1.0	2274±27	2135±3
2		2182±16	1888±201
3		2110±10	1668±6
4		1988±20	1041±79
5		1862±90	694±5
6		1827±38	396±166
7		1076±22	327±3
8		982±100	287±6
9		906±37	281±33
10		418±167	263±5

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Table (6): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 5.0 % Tween 20 using hot homogenization technique and emulsion solvent injection technique at 12,000 rpm.

GMS % w/w	Tween 20 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	5.0	2170±49	1381±12
2		1823±21	1346±4
3		1606±52	1237±57
4		1594±4	784±97
5		1522±50	453±25
6		871±79	237±2
7		621±63	210±0.57
8		375±104	204±1
9		338±178	202±1.3
10		231±11	198±5.19

Table (7): particle diameter of nanoparticles formulations prepared using glyceryl monostearate (GMS) and 0.5 % Tween 80 using hot homogenization technique and emulsion solvent injection technique at 6,000 rpm.

GMS % w/w	Tween 80 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	0.5	3099±35	3016±310
2		2789±25	2752±2
3		2639±7	2543±15
4		2557±107	2512±54
5		2502±1.5	2492±34
6		2456±190	2239±3
7		2359±2	2199±52
8		2324±1	2027±2
9		2309±4	1924±1
10		2281±7	729±29

Table (8): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 1.0 % Tween 80 using hot homogenization technique and emulsion solvent injection technique at 6,000 rpm.

GMS % w/w	Tween 80 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	1.0	2819±26	2771±5
2		2724±19	2450±4
3		2524±9	2226±48
4		2412±67	2222±74
5		2388±10	2017±25
6		2338±22	2009±18
7		2320±137	975±52
8		2273±18	948±5
9		2165±12	770±55
10		2070±5	354±39

Table (9): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 5.0 % Tween 80 using hot homogenization technique and emulsion solvent injection technique at 6,000 rpm.

GMS % w/w	Tween 80 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	5.0	2074±6	2072±14
2		2029±4	2004±158
3		1693±5	1137±18
4		1461±4	1001±131
5		1329±29	973±21
6		1314±6	528±49
7		1308±11	411±25
8		1196±12	410±32
9		1193±23	378±64
10		1069±2	297±4

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Table (10): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 0.5 % Tween 80 using hot homogenization technique and emulsion solvent injection technique at 12,000 rpm.

GMS % w/w	Tween 80 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	0.5	2881±27	2736±88
2		2785±45	2759±293
3		2558±39	2486±10
4		2483±53	2298±23
5		2480±5	2274±25
6		2408±43	2251±77
7		2340±34	2215±21
8		2289±3	1857±24
9		2196±14	1010±135
10		2190±13	490±43

Table (11): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 1.0 % Tween 80 using hot homogenization technique and emulsion solvent injection technique at 12,000 rpm.

GMS % w/w	Tween 80 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	1.0	2636±15	2611±9
2		2510±40	2448±1
3		2359±24	2279±163
4		2163±27	2096±20
5		1975±29	1674±17
6		1813±21	1403±33
7		1743±99	982±154
8		1638±68	718±40
9		861±45	610±48
10		359±112	259±39

Table (12): particle diameter of nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 5.0 % Tween 80 using hot homogenization technique and emulsion solvent injection technique at 12,000 rpm.

GMS % w/w	Tween 80 % w/w	Particle diameter (nm)± S.D(hot homogenization)	Particle diameter (nm)± S.D(emulsion solvent injection)
1	5.0	810±1	480±17
2		240±1	234±35
3		237±1	233±1.5
4		228±0.57	224±16
5		221±0.57	218±14
6		211±19	193±74
7		200±2.8	188±21
8		193±1.5	183±81
9		191±0.57	182±12
10		187±0.57	156±76

2. Effect of viscosity of the dispersion medium:

Figures (1-12) showed that increasing viscosity of the aqueous phase by various concentration of glycerol (10, 30, 50 % w/w) for both Tween 20 and Tween 80 surfactants and GMS concentrations range from (1- 10 % w/w) leads to marked decrease of SLN particle size. These results were agreed with that obtained from Ghorab *et al* [10, 11]. These results suggest that increasing viscosity of the outer phase increase the impact rate between the lipid and the external phase, leading to decrease in particle size.

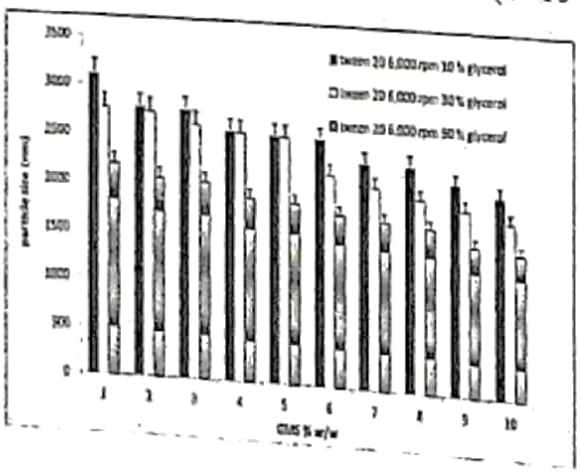

Fig (1): effect of viscosity on particle diameter of solid lipid nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 0.5 % w/w Tween 20 using hot homogenization technique at 6,000 rpm.

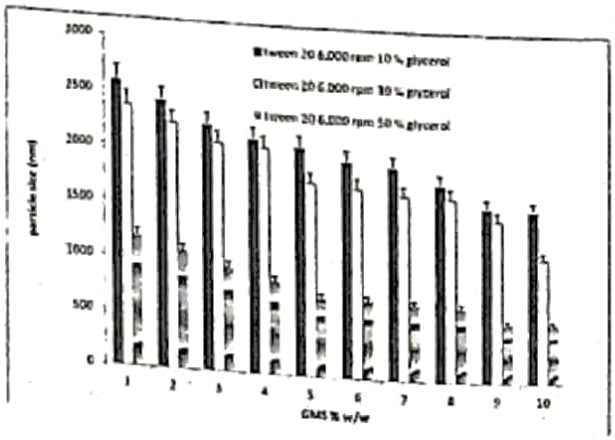

Fig (2): effect of viscosity on particle diameter of solid lipid nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 1.0 % w/w Tween 20 using hot homogenization technique at 6,000 rpm

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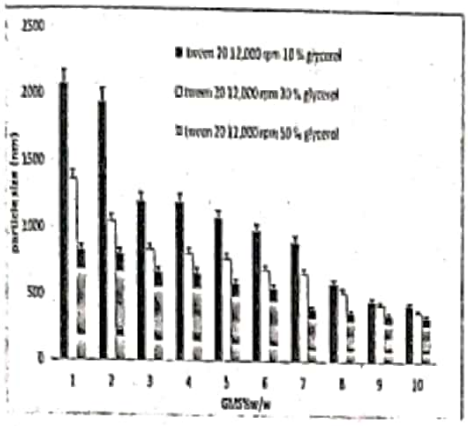


Fig (3): effect of viscosity on particle diameter of solid lipid nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 5.0 % w/w Tween 20 using hot homogenization technique at 6,000 rpm.

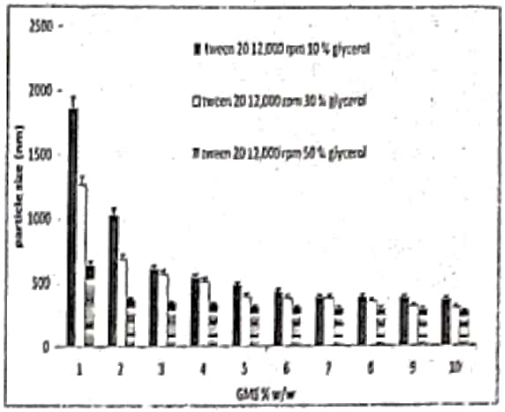
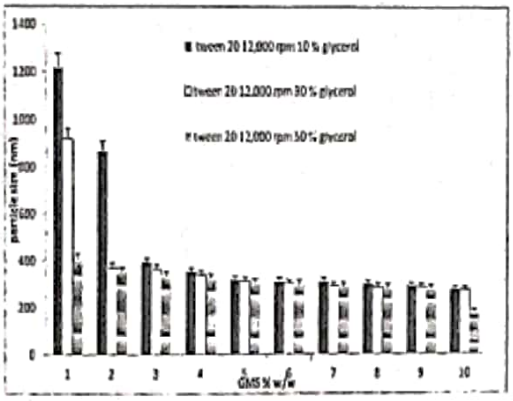


Fig (4): effect of viscosity on particle diameter of solid lipid nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 0.5 % w/w Tween 20 using hot homogenization technique at 12,000 rpm.



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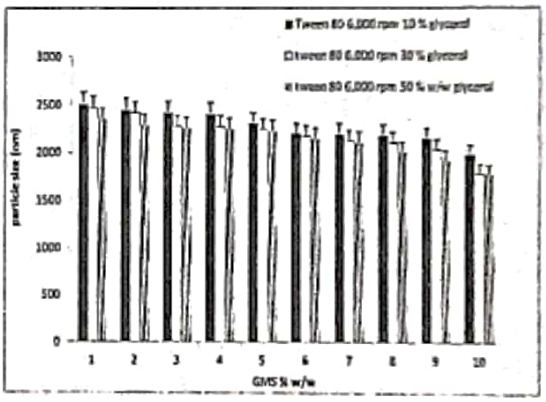

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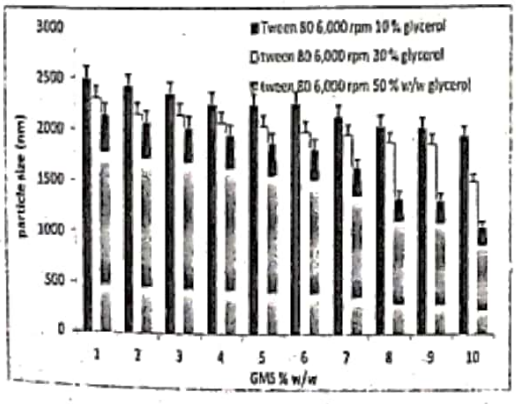
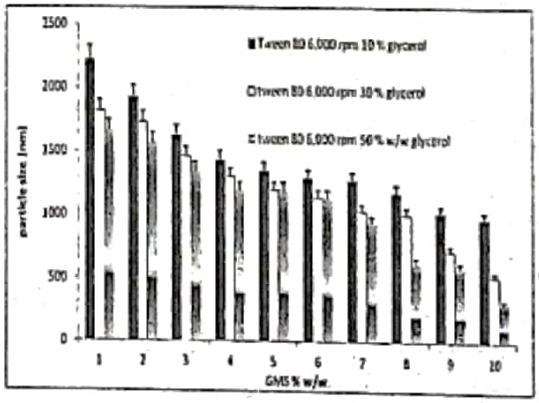


Fig (7): effect of viscosity on particle diameter of solid lipid nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 0.5 % w/w Tween 80 using hot homogenization technique at 6,000 rpm.



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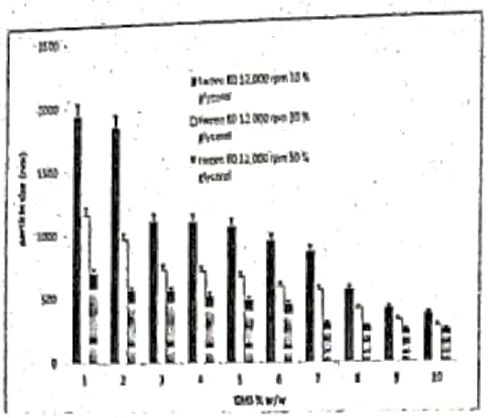

Fig (9): effect of viscosity on particle diameter of solid lipid nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 5.0 % w/w Tween 80 using hot homogenization technique at 6,000 rpm.

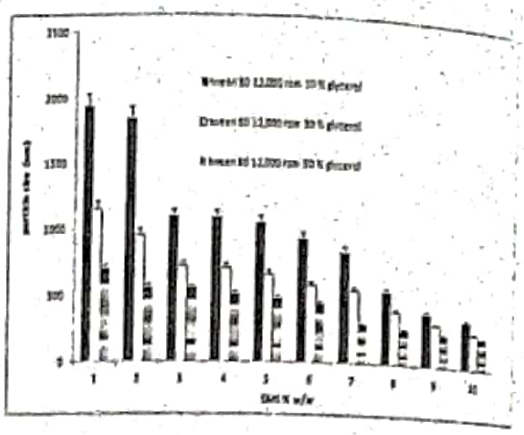

Fig (10): effect of viscosity on particle diameter of solid lipid nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 0.5 % w/w Tween 80 using hot homogenization technique at 12,000 rpm.

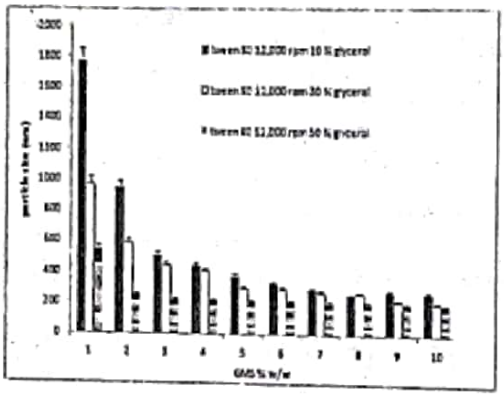

Fig (11): effect of viscosity on particle diameter of solid lipid nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 1.0 % w/w Tween 80 using hot homogenization technique at 12,000 rpm.

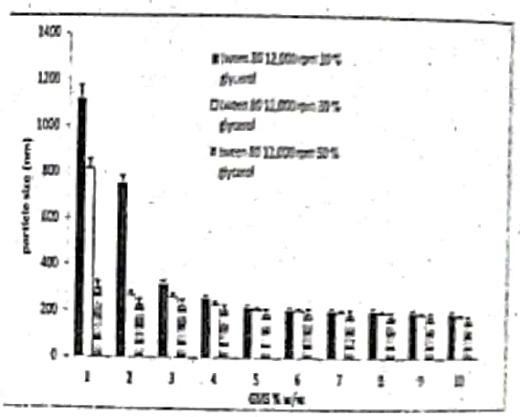

Fig (12): effect of viscosity on particle diameter of solid lipid nanoparticles formulations prepared using Glyceryl monostearate (GMS) and 5.0 % w/w Tween 80 using hot homogenization technique at 12,000 rpm.

3. Effect of homogenization speed on the size of formed solid lipid nanoparticles

It is reasonable to increase homogenization speed in order to reduce particle size of formed solid lipid nanoparticles. The high speed accompanied by time is very important factor for the resulted particles. Longer time may cause instability for colloidal particles due to high input of energy that leads to aggregation of colloidal particles into larger microparticles. Shorter periods of homogenization may fail to produce nanoparticles. The medium duration of homogenization is advantageous. This is because appropriate heat provided in the preparation process will lead to stability of formed particles with uniformity of size, homogeneity of shape and stability of formed colloidal particles after production [12].

Solid lipid nanoparticles using high shear hot homogenization and modified emulsion solvent injection technique using homogenization speed of 6,000 rpm or 12,000 rpm were prepared using Glyceryl monostearate as lipid core with concentrations

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range from 1- 10 % w/w . The lipid nanoparticles were emulsified with Tween 20 or Tween 80 with concentrations (0.5, 1, 5 %w/w) and stabilized with 1% lecithin in all formulations.

As seen in figures (13-24), it was found that the increase in homogenization speed form 6,000 rpm to 12,000 rpm had an effect on size of formed solid lipid nanoparticles. The particle size was reduced for all formulas, and in some cases, to be transferred from micron range to be of submicron range. Trotta et al [13] prepared microparticles of Glyceryl monostearate and isobutyric acid and found that high shear homogenization will reduce the size of produced particles to be of submicron range, which augment our results, this is may be due to higher homogenization speed may have influence on the collision of particles accompanied with enforcing between rotor and stator of homogenizer. Results showed that particle sizes of solid lipid nanoparticles of most formulations prepared with help of 12,000 rpm as the homogenization speed are of nanosize. These results were agreed with that results of Liu et al and Hazendar and dortunc [14,15] who stated that at a stirring speed below 600 rpm, the uniformity of the mixing force throughout the emulsion mixture decreased, and the homogeneous suspension was not obtained. In contrast, stirring speeds higher than 800 rpm were vigorous and uniform enough to form small and homogeneous size distribution nanoparticles. Vivek et al [16, 17] studied the effect of homogenization pressure on size of produced solid lipid nanoparticles using glyceryl monostearate and found that increase of homogenization pressure from 5000 psi to 10,000 psi reduced mean diameter. Reduction in particle size is mainly due to the development of cavitational forces in the homogenization gap, resulting in diminution of the lipid droplets to the nano size.

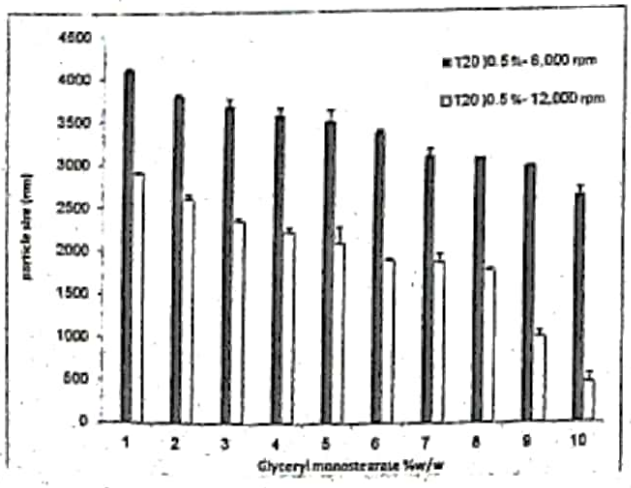

Fig (13): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 0.5 % w/w Tween 20 using hot homogenization technique.

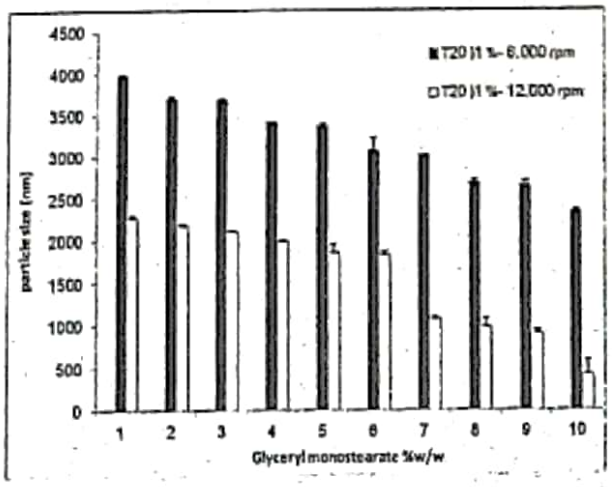

Fig (14): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 1.0 % w/w Tween 20 using hot homogenization technique.

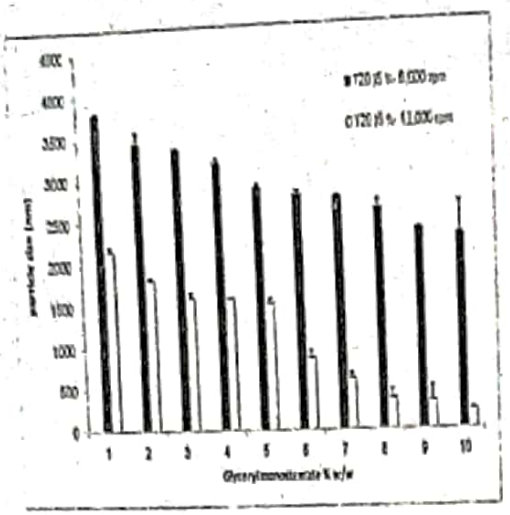

Fig (15): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 5.0 % w/w Tween 20 using hot homogenization technique.

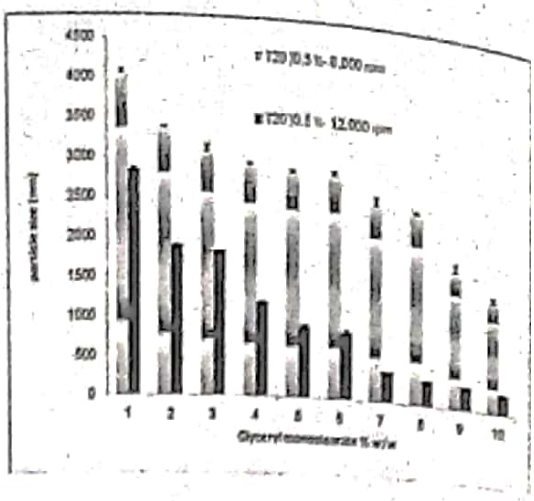

Figure (16): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 0.5 % w/w Tween 20 using emulsion solvent injection technique.

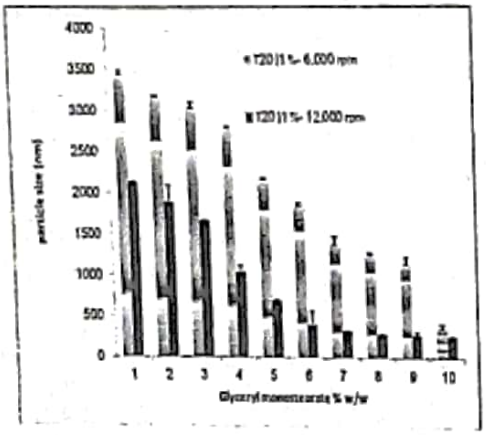

Figure (17). effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 1 0 % w/w Tween 20 using emulsion solvent injection technique.

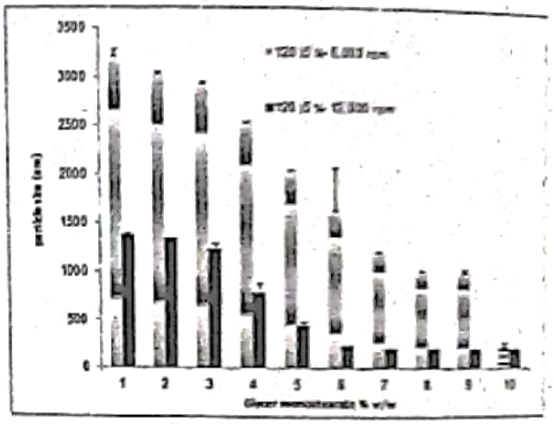

Figure (18): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 5 0 % w/w Tween 20 using emulsion solvent injection technique.

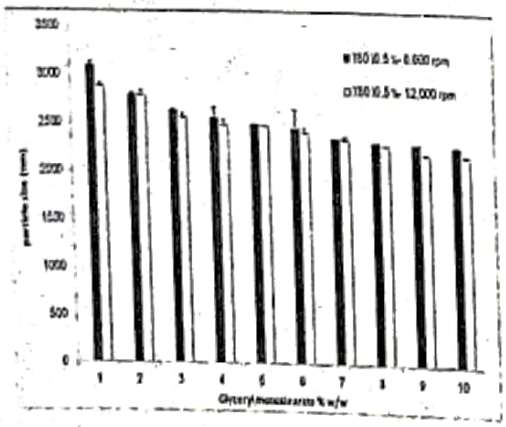

Fig (19): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 0.5 % w/w Tween 80 using hot homogenization technique.

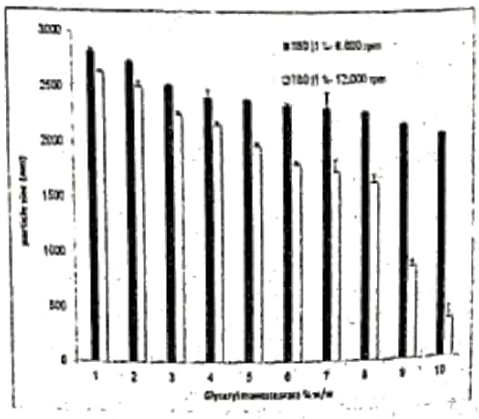

Fig (20): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 1.0 % w/w Tween 80 using hot homogenization technique.

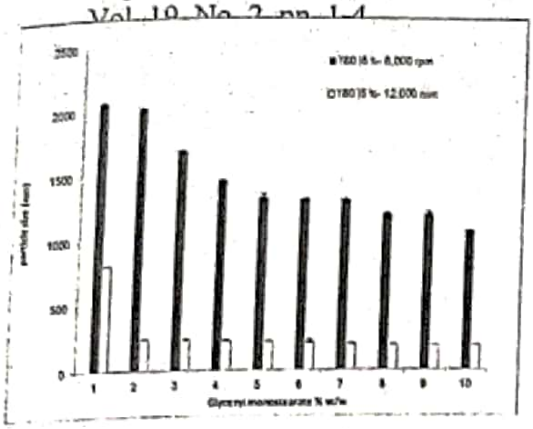

Fig (21): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 5 0 % w/w Tween 80 using hot homogenization technique.

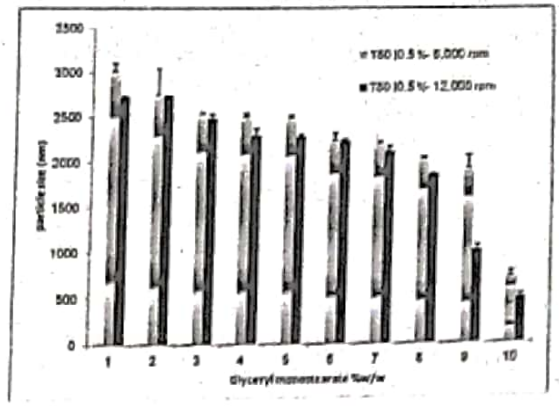

Fig (22): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 0.5 % w/w Tween 80 using emulsion solvent injection technique.

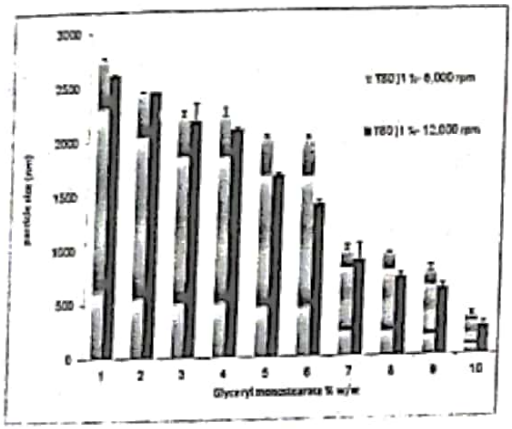

Fig (23): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 1.0 % w/w Tween 80 using emulsion solvent injection technique.

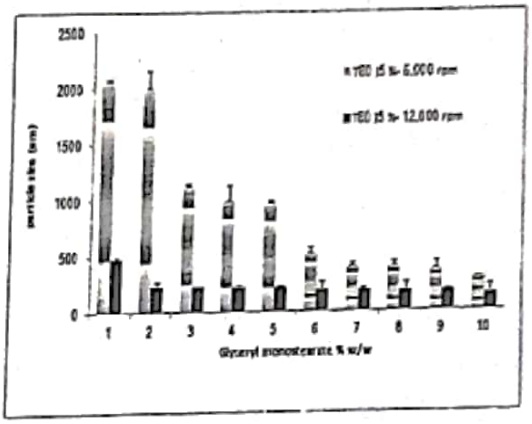

Fig (24): effect of homogenization speed on particle size of solid lipid nanoparticles prepared with Glyceryl monostearate and 5.0 % w/w Tween 80 using emulsion solvent injection technique.

CONCLUSION

Particle diameter of solid lipid Nanoparticles prepared with Glyceryl monostearate and Tween 20 or Tween 80 as surfactants and lecithin as co-surfactants affected by variation of process parameters such as methods of preparation, viscosity of dispersion medium and speed of homogenization.

Solid lipid nanoparticles were successfully prepared by high shear hot homogenization and emulsion solvent injection techniques. Glycerol used as viscosity imparting agent produced solid lipid nanoparticles of smaller diameter. Increasing speed of homogenization in the hot homogenization and emulsion solvent injection techniques was found to reduce the size of produced solid lipid nanoparticles.

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تحضير و توصيف الجزيئات الدقيقة ذات الأوساط الدهنية الصلبة

II-تأثير اللزوجة، طريقة التحضير، و معدل التقليب على الخواص الفيزيائية للجزيئات الدهنية ذات الأوساط الصلبة

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تهدف هذه الدراسة لقياس أفضل العوامل الخاصة بتحضير الجزيئات الدقيقة ذات الأوساط الصلبة من مادة جلسريل احادى الستيرات و الذي تتميز بكونها متوافقة حيويا و سهلة الايض داخل الجسم. تم دراسة عدة عوامل و مدى تأثيرها على الخواص الفيزيائية للجزيئات الدهنية ذات الأوساط الصلبة و ابرزها مقياس قطرالجزيئات. من أهم هذه العوامل دراسة تأثير اللزوجة، طريقة التحضير، و معدل التقليب. تم تحضير الجزيئات الدقيقة ذات الأوساط الصلبة بطريقتين هما : طريقة التقليب الساخن باستخدام معدلات سرعة مختلفة. و كذلك طريقة حقن المذيب لتكوين المستحلب. وقد وجد ان طريقة التحضير باستخدام طريقة حقن المذيب تنتج جزيئات دهنية زات قطر اصغر. بالإضافة إلى ذلك، تم دراسة تأثير اللزوجة على تكوين الجزيئات الدقيقة و وجد ان زيادة اللزوجة تؤدى الى تكوين جزيئات ذات اقطار اصغر تصل الى المقياس النانوى . و بالنسبة لمعدل التقليب ، فان زيادة هذا المعدل من 6,000 لفة /دقيقة الى 12,000 لفة /دقيقة ينتج جزيئات دهنية دقيقة نانوية ذات اقطار اصغر.