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Research Article

EVALUATION OF DIFFERENT GRADES OF GUAR GUM, ACACIA GUM, AND POLYVINYL PYRROLIDONE AS CROSS-LINKERS IN PRODUCING SUBMICRON PARTICLES

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ABSTRACT

Objective: The main goal of this research is to evaluate using of guar gum (GG), Arabic gum, and poly-vinylpyrrolidone, each of two viscosity grades, as crosslinking agents in producing nanoparticles and submicron particles.

Methods: The method used is the preparation of nanoparticles of carbamazepine using two viscosity grades of polymers (GG, acacia gum, and polyvinyl pyrrolidine) by emulsification/solvent evaporation technique. Based on a statistical design composed of mixed 32-levels factors and 13-levels factor was selected for screening and preliminary optimization purposes. The collected nanoparticles from the first portion of all 24 runs were subjected to the following qualifications, particle diameter, polydispersity index (PDI%), zeta potential, entrapment efficiency (EE%), and drug loading.

Results: The study revealed that based on the obtained findings and the associated statistical analysis, influences of stirring rate, polymer type, polymer grade, and polymer loading in different formulation runs resulted in produced particles with different characteristics such as particle size of different formulation series are in sub-micron (0.13–91.83 μm) with EE% (max 52.28%), reduced EE observed in this study can be attributed to lower polymer load in the dispersed phase (1% and 10%) and zeta potential values were small (range 35.69–41.68), all preparation factors have no significant effect on zeta potential, PDI values (close to zero) showed that all the samples formed monodispersions in water and its due to steric hindrance than a surface charge.

Conclusion: The study recommends that different polymers need special techniques for producing cross-linked particles with sub-micron particles, no universal technique can be applied. Keywords: Polymer, Guar gum, Acacia gum, Polyvinyl pyrrolidine, Carbamazepine, Emulsification/solvent evaporation technique, Stirring rate.

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INTRODUCTION

Nanotechnology is the science that deals with the processes that occur at a molecular level and of nanolength scale size [1].

Nanotechnology by manipulation of characteristics of materials such as polymers and fabrication of nanostructures can provide superior drug delivery systems for better management and treatment of diseases. The nanostructures employed as drug delivery systems have multiple advantages which make them superior to conventional delivery systems [2].

Polymeric nanoparticles

Polymeric nanoparticles are colloidal solid particles with a size range of 10–1000 nm 1 and they can be in a spherical, branched, or shell structure. They are developed from non-biodegradable and biodegradable polymers. The first fabrication of nanoparticles was about 35 years ago as carriers for vaccines and cancer chemotherapeutics [3].

Polysaccharide nanoparticles by crosslinking

Preparation of polysaccharide nanoparticles by crosslinking can be achieved by either ionic crosslinking (physical crosslinking) or covalent crosslinking (chemical crosslinking) [4].

Guar gum (GG)

GG is galactomannan derived from Guar Cyamopsis tetragonolobus kernels which belong to the family, *Leguminosae*. GG can produce highly viscous, pseudoplastic aqueous solutions even at low concentrations due to the high molecular weight (up to 200,000–300,000 Daltons) and the presence of the extended repeating unit formed by hydrogen bonding. This feature allows GG to be soluble and forms gel even in cold water [5].

Thermal treatment of GG at 700 for 10 min is an efficient means to produce GG with the desired properties for pharmaceutical processing and industries. Such treatment has resulted in the production of treated GG with improved flowability, swellability, and compressibility. On the other hand, the method of drying seems to have a significant influence on the viscosity of the produced guar powder and verification of such effect might necessitate a more collaborated extended study [6].

Acacia gum

This is the dried exudate of the acacia tree (Acacia Senegal or related species of Acacia Fam. *Leguminosae*). It is a complex mixture of Ca, Mg, and K salts of Arabic acid (a complex, highly branched polysaccharide colloid) that contains galactose, rhamnose, glucuronic acid, 4-O-methyl glucuronic acid, and arabinose residues; it shows a broad molecular weight distribution. The gum is highly soluble in water, and solutions of up to 50% gum concentration can be prepared [7].

Povidone (PVP)

PVP is a water-soluble pharmaceutically acceptable polymer. Due to its ability to improve solubility and wettability of poorly soluble drugs,

it is frequently used in solid dispersions to enhance solubility and dissolution rate [8,9]. Due to its hydrophilicity and rapid dissolution in an aqueous medium, PVP is largely applied as a carrier in immediate release dosage forms.

Carbamazepine (CBZ)
CBZ or 5H-Dibenz[b,f]azepine-5-carboxamide is a white or almost white crystalline powder. It is very slightly soluble in water; sparingly soluble in alcohol and acetone, and freely soluble in dichloromethane.

Although CBZ has a high intestinal permeability, its bioavailability is limited by its low water solubility (0.11 $mgmL^{-1}$) [10].

Polysaccharide nanoparticles by crosslinking
Preparation of polysaccharide nanoparticles by crosslinking can be achieved by either ionic crosslinking (physical crosslinking) or covalent crosslinking (chemical crosslinking). Covalently crosslinked polysaccharide nanoparticles enable the network structure to be permanent since irreversible chemical links are formed unless biodegradable or stimuli-responsive crosslinkers are employed. The rigid network allows the absorption of water and bioactive compounds without the dissolution of the nanoparticles even when the pH drastically changes [4]. Physical crosslinking of polysaccharides is based on ionic interactions between charged polysaccharides and ionic crosslinkers. This method gives nanoparticles reversibility and is considered biocompatible due to the lack of harsh preparation conditions or toxic crosslinkers. Ionically-crosslinked nanoparticles are generally pH-sensitive, which is a suitable feature for stimuli-sensitive controlled release. The introduction of hydrophobic segments into hydrophilic polysaccharide backbones enables the formation of self-assembled structures such as micelles, particles, and hydrogels [4]. By manipulating the introduction condition such as polysaccharide/hydrophobic segments' molar ratios and the lengths of polysaccharides and hydrophobic segments, nanoparticles are formed to minimize interfacial free energy. The introduction of hydrophobic segments into polysaccharides is achieved by grafting hydrophobic groups from hydroxyl, amino, or carboxyl groups of the polysaccharide main chains. These chemically modified amphiphilic macromolecules can self-associate in an aqueous solution by intra and/or intermolecular hydrophobic interaction, which can form nanoparticles [11]. Water-insoluble drugs are solubilized and encapsulated within the hydrophobic core and become soluble in water due to the hydrophilic shell. The drugs are then released from the inner core of the nanoparticles through outer stimuli changes such as pH, temperature, and ionic strength. Recently, there have been several studies on the syntheses of polysaccharide-based self-aggregated nanoparticles for drug delivery systems [12].

The objective of this study is to evaluate using of GG, Arabic gum, and poly-vinylpyrrolidone, each of two viscosity grades, as crosslinking agents in producing nanoparticles and submicron particles.

METHODS

Materials
The following materials have been utilized during the experimental part of the research:

Material	Specifications	Source
Carbamazepine	Pharmaceutical grade	Bajaj Health care Ltd
Guar gum	Pharmaceutical grade, expiry 05/2018	Reliance Industries (Pakistan)
Povidone PVPK30	Pharmaceutical grade	BoaiNKY pharmaceuticals
Povidone PVPK90	Technical grade	~ ~
Acacia gum (117cps)	Analytical grade	Avonchem (England)
Acacia gum (128cps)	Analytical grade	Panreac (Germany)
Ethyl acetate	Analytical grade	Winlab

Treated GG was prepared through the thermal treatment method as described by Yagoub and Nur [13].

The following instruments were used in the experimental part of the research:

Instrument	Specification and Source
Analytical balance	Reblab ®, Germany
Zetasizer 90 plus	Malvern Panalytical Ltd
U.V. Spectrophotometer	double beam UV-1800, Shimadzu, Japan
Magnetic stirrer	Stuart, England
Scanning electron microscope	Zeiss EVO LS10; Cambridge, United Kingdom

Methods
Experimental design
Based on the aim of this project, a statistical design composed of mixed 32-levels factors and 13-levels factor was selected for screening and preliminary optimization purposes [14].

Throughout the design, three factors, namely, stirring rate (SR), polymer level, and polymer amount were examined at two levels whereas the fourth factor (polymer type [PT]) was investigated at three different levels. All factors were investigated for their main and interactive influences on the properties of produced nanoparticles and tablets. Consequently, an experimental design composed of a total of 24 formulation runs was thus generated (Table 1). Within the design, the axial points represented the extreme settings for each factor while the central point setting for each factor coordinated in replication was to estimate the error.

Method of nanoparticle preparation
The emulsification/solvent evaporation technique involves two steps [15,16]. The first step requires emulsification of the polymer solution into an aqueous phase. This was done by dissolving each polymer according to run (GG, Acacia, or PVP) in ethyl acetate as organic solvent then CBZ was added to the solution with stirring at a specified rate associated with each run (1000 or 500 rpm) for 90 min. The polymer organic solution containing the dissolved drug was dispersed into nanodroplets. In the second step, formed nanodroplets were kept in a hood for vacuum drying at room temperature for complete solvent evaporation and induction of polymer precipitates in the form of nanospheres in which the drug is finely dispersed in the polymer matrix network.

Nanoparticles characterization
Collected nanoparticles from the first portion of all runs were subjected to the following qualifications.

Particle size analysis
Using particle size analyser 90, measurements of polydispersity (PD %), particle diameter (nm), and zeta potential (mv) were performed.

A specified amount of dry particles was completely dissolved in ethyl acetate, filtered, and transferred to the instrument cell and subjected to the test [17].

Entrapment efficiency (EE) of nanoparticles
Dried nanoparticles were dissolved in ethyl acetate (a common solvent for polymers and drug samples). The amount of entrapped CBZ that was present in the solution was measured spectrophotometrically at 287 nm (USP [18]).

Drug incorporation efficiency was expressed as drug content (% w/w), also referred to as drug loading in the literature, and drug entrapment (%); represented by Equations. (1) and (2), respectively. The individual

Table 1: Layout of formulation runs according to mixed 32-levels factors and 13-levels factor statistical design

Run	Stirring Rate	Polymer grade	Polymer load (%)	Polymer type
R1	1000	G-non treated	1	Guargum
R2	1000	Acacia lower viscosity	1	Acacia Gum
R3	1000	PovidoneK90 higher viscosity	1	Povidone
R4	1000	G-non treated	10	Guargum
R5	1000	Acacia lower viscosity	10	Acacia Gum
R6	1000	PovidoneK90 higher viscosity	10	Povidone
R7	1000	G- treated	1	Guargum
R8	1000	Acacia higher viscosity	1	Acacia Gum
R9	1000	PovidoneK30 lower viscosity	1*	Povidone
R10	1000	G- treated	10	Guargum
R11	1000	Acacia higher viscosity	10	Acacia Gum
R12	1000	PovidoneK30 lower viscosity	10	Povidone
R13	500	G-non treated	1	Guargum
R14	500	Acacia lower viscosity	1	Acacia Gum
R15	500	PovidoneK30 lower viscosity	1	Povidone
R16	500	G-non treated	10	Guargum
R17	500	Acacia lower viscosity	10	Acacia Gum
R18	500	PovidoneK90 higher viscosity	-10	Povidone
R19	500	G- treated	1	Guargum
R20	500	Acacia higher viscosity	1	Acacia Gum
R21	500	PovidoneK30 lower viscosity	1	Povidone
R22	500	G- treated	10	Guargum
R2*3	500	Acacia higher viscosity	10	Acacia Gum
R24	500	PovidoneK30 lower viscosity	10	Povidone

values for two replicate determinations and their mean values were reported.

- Drug loading (% w/w) =Mass of the drug in nanoparticles Mass of nanoparticle%100 (1)
- Drug Entrapment (%) = Mass of the drug in nanoparticles Mass of drug used in formulation%100 (2).

Electron microscopic scan

Micrographs of the samples were taken using a scanning electron microscope (SEM). Samples were fixed on stubs using both sides of adhesive carbon tape (SPI Supplies, West Chester, USA) and coated under vacuum with gold in a Q150R sputter coater unit from Quorum Technologies Ltd. (East Sussex, United Kingdom) in an argon atmosphere at 20 mA for 60 s [19].

RESULTS

Composition and layout of formulations

Table 1 shows the layout and iterations of different formulation runs in the selected different-level experimental design.

Characterization of produced particles

Table 2 summarizes size diameter, polydispersity index (PDI%), zeta potential, drug loading, and EE% properties of produced particles within different formulation runs whereas the morphology of produced particles is presented in Figs. 1-6.

Table 2: Size diameter, polydisperse index (PDI%), zeta potential (ζ), (EE%), and drug loading properties of yielded particles within different formulation runs

Run No.	Drug loading (%)	EE (%)	Diameter (μm)	PDI (%)	ζ (mV)
R1	26.1	52.3	0.77	5.50	–38.22
R2	26.1	52.3	38.20	0.52	–36.11
R3	26.1	52.3	1.45	1.76	–39.01
R4	6.5	13.1	26.45	0.37	–40.34
R5	6.5	13.1	1.43	0.50	–35.86
R6	6.5	13.1	6.97	0.43	–40.71
R7	26.1	52.3	4.68	0.62	–37.08
R8	26.1	52.3	2.76	0.30	–38.40
R9	26.1	52.3	13.75	0.67	–39.77
R10	6.5	13.1	2.63	0.39	–37.58
R11	6.2	12.5	6.09	4.04	–41.68
R12	5.9	11.8	10.73	0.40	–38.63
R13	19.8	39.6	4.71	0.55	–38.67
R14	23.5	47.0	90.75	0.44	–37.87
R15	22.5	45.0	41.06	0.69	–37.85
R16	6.4	12.7	3.60	0.38	–35.69
R17	6.5	13.1	91.83	1.09	–35.75
R18	6.5	13.1	9.67	1.04	–37.61
R19	26.1	52.3	0.13	0.09	–37.15
R20	26.1	52.3	2.16	0.38	–37.99
R21	26.*1	52.3	6.35	0.56	–36.80
R22	6.5	13.1	0.17	1.74	–38.83
R23	6.5	13.1	18.11	0.81	–39.90
R24	6.5	13.1	16.64	0.54	–37.08

DISCUSSION

The discussion would focus on the influences of factors in the design on attributes of produced particles of CBZ within different runs.

Influences of investigated design factors on characteristics of yielded particles

Based on the obtained findings and the associated statistical analysis, different formulation runs result in produced particles with different characteristics. The following subsections aim to discuss influences and variations associated with characteristics of produced particles of different formulation runs.

Effects on particles' size diameter

From the results presented in Table 2, different formulation runs produced particles with diameters varied between submicron and micron range (0.13–91.83 μm). Such variation in particles' diameter around the average diameter value appears statistically sound (p=0.003 at CI95%). Among different variables investigated for their influences on the attained particle diameters, only PT measures a considerable individual quadratic (Q) effect (Table 3). A remarkable decrease in particle diameter (from micron to submicron region) was evidenced with treated GG (R19 and R22) and, to some extent, with PVP k_{90} (R3 and R6) as shown in Table 2. This is supported by the distance weighted least-squares fit of the relation between particles diameter and the utilized polymers depicted in Fig. 7.

Among different variables investigated for their possible influences on the size of yielded particles, PT measures the statistically significant impact on particles' size through its quadratic (Q) effect (p=0.043, Table 3). On this occasion, formulation runs incorporating native or treated GG as matrix agents (especially R 19 and R 22) are shown to be associated with the smallest particles' size as compared to other grades or types of polymers investigated (Table 2 and Fig. 7).

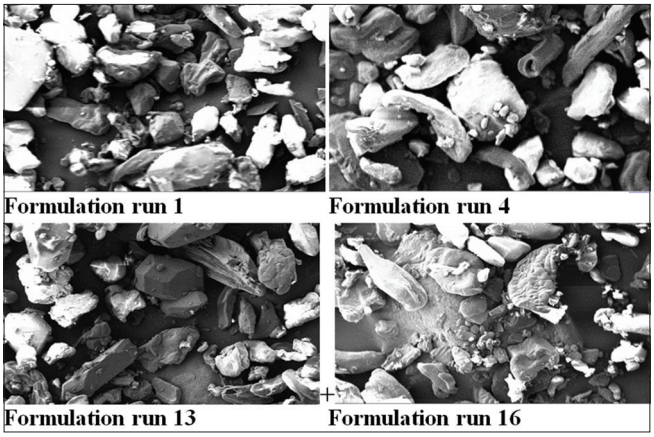

Fig. 1: Scanning electron microscopic images showing shape and surface morphology of yielded particles in formulation runs comprised of native guar gum

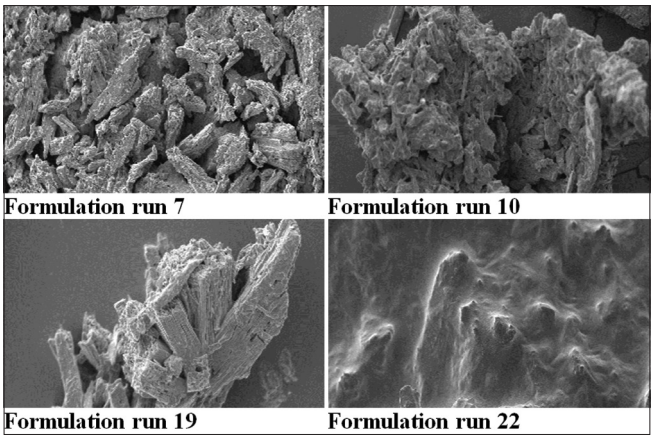

Fig. 2: Scanning electron microscopic images showing shape and surface morphology of yielded particles in formulation runs comprised of treated guar gum

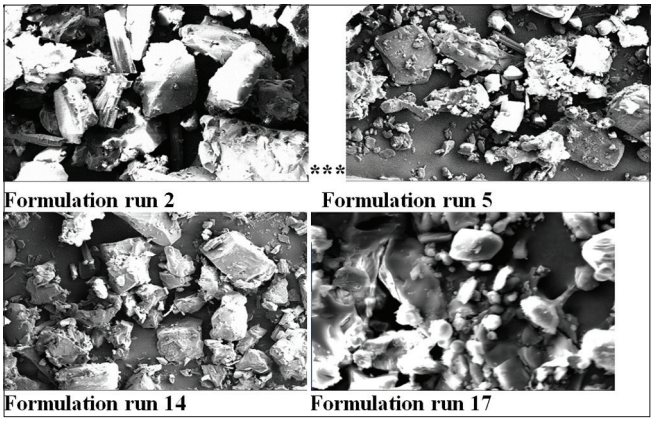

Fig. 3: Scanning electron microscopic images showing shape and surface morphology of yielded particles in formulation runs comprised of low viscosity (117 cps) acacia gum

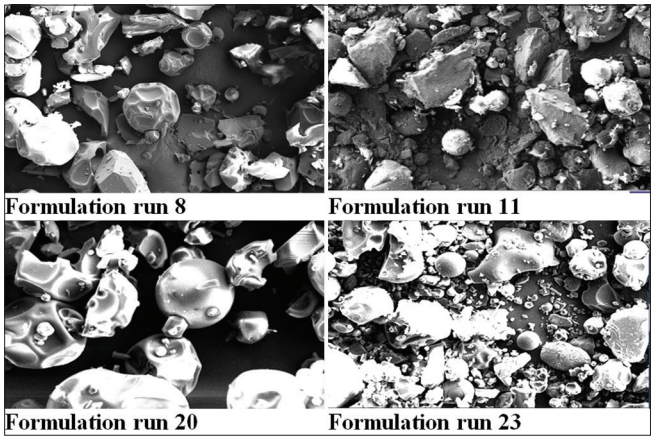

Fig. 4: Scanning electron microscopic images showing shape and surface morphology of yielded particles in formulation runs comprised of high viscosity (128 cps) acacia gum

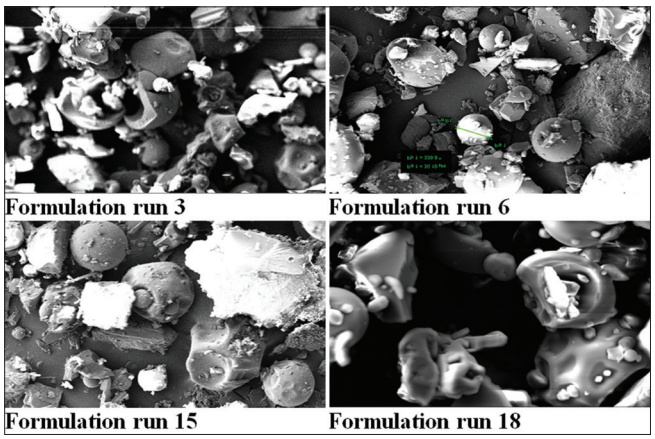

Fig. 5: Scanning electron microscopic images showing shape and surface morphology of yielded particles in formulation runs comprised of povidone-k30

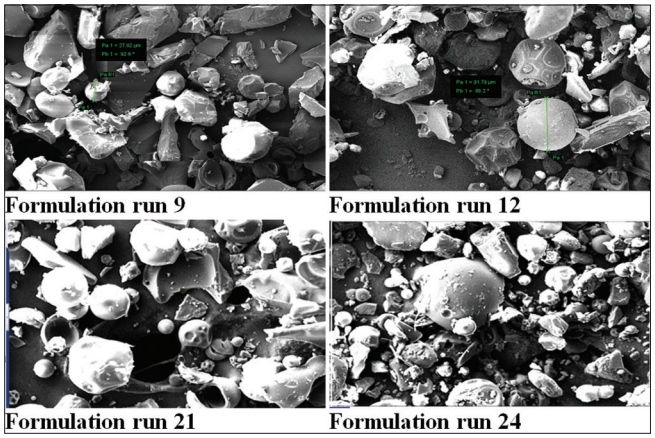

Fig. 6: Scanning electron microscopic images showing shape and surface morphology of yielded particles in formulation runs comprised of povidone-k90

GG is expected to reduce particle size because its polymer chain has weak mechanical strength that can be broken by the stirring effect [18]. In treated GG, the effect is predominant due to heat treatment which leads to segmentation of the polymer chain.

The effect of SR on the size of the produced particles is differing according to PT and this may be attributed to the internal phase viscosity [20]. Table 3 indicates a comparative noticeable influence on particle size caused by the joined influence of SR and utilized polymer grade (PG), especially at a SR of 1000 rpm. Although the joined influence is not that sizeable for statistical consideration, it strongly supports the idea that the application of high stirring speed could provide the high shearing force needed to break down the drug-polymer droplets into

Table 3: Summary of influences of linear (L), quadratic (Q) and interactive settings of stirring rate (SR), polymer type (PT), polymer grade (PG), and polymer loading (PL) on some properties of produced particles within different formulation runs

Factors setting	Size diameter		ζ potential		EE%		Drug load	
	Effect	p	Effect	p	Effect	P	Effect	p
(1) SR (L)	−10795	0.312	−0.904	0.194	0.016	0.143	0.008	0.143
(2) PT (L)	2971	0.821	−0.607	0.470	0.011	0.386	0.007	0.386
(3) PG (L)	−22179	0.057	−1.134	0.117	0.019	0.089	0.009	0.090
(4) PL (L)	2272	0.830	−0.303	0.652	−0.377	0.001	−0.188	0.001
PT (Q)	24542	0.043	0.291	0.680	0.003	0.761	0.002	0.761
1L×2L	−3377	0.796	−0.617	0.462	−0.014	0.272	−0.007	0.272
1L×3L	11052	0.315	0.184	0.789	−0.018	0.107	−0.010	0.107
1L×4L	−3491	0.741	−0.713	0.299	−0.108	0.094	−0.011	0.095
2L×3L	−2150	0.873	−0.689	0.427	−0.010	0.472	−0.005	0.472
2L×4L	−182	0.989	0.207	0.803	−0.014	0.301	−0.007	0.301
3L×4L	4337	0.688	−1.050	0.144	−0.018	0.119	−0.009	0.118

p is the associated statistical probability for significant effect at $P \leq 0.05$

smaller particles [21]. It should be, however, noted that the effect of SR on particle size in some runs that incorporate treated GG (R 7, R10, R19, and R22) is proportional where an increase in produced particle size is anticipated in consequence of increasing the SR as summarized in Table 2. In this instance, such an effect of SR on particle size might relate strongly to polymer properties and the influences of mechanical strength on the utilized polymer.

The viscosity of the medium has a larger impact on the properties of produced particles, and these viscosities are dependent on the used PG. Viscosity is associated with the strong mechanical strength of the polymer chain that resists the effect of SR in decreasing the particle size. These effects, though not statistically considered, are evident by the comparative large magnitude of the effect of PG on particle size as included in Table 3 (−22179, p=0.057).

The degree of particle aggregation in a liquid medium can be determined by the PDI, values close to zero being favorable as opposed to those close to one, which indicates a high degree of aggregation [22]. With GG, R19 showed the least polydispersity (0.094, Table 2), so it has uniform distribution along with the solution which can be explained by the decreased internal viscosity of gum in response to thermal treatment that breaks the polymer chain and, thus, decreases the viscosity which is supported by findings of relative published work [23].

Concerning acacia gum, the smallest particle achieved with 1000 rpm and 10% polymer load (R5, Table 2) wherein this case, the effect of SR appears predominant over polymer load due to the lower viscosity acacia gum is used in R17 with the same polymer load 10% and different SR 500rpm and produce larger particle than R5 Table 2 but this not approved statistically as in Table 3, the SR has no significant effect on particle size. However, the lowest polydispersity has been observed in R 14 (0.442, Table 2) with production settings of 500 rpm and 1% polymer load that results in the production of comparative large particles (90,753.68 µm), this, in turn, could be attributed to increasing particle size in association with reduction of particle agglomeration.

With PVP, the largest particles produced are associated with R15 that utilizes PVP k_{30} as crosslinking polymer and the smallest one is related to R3 which incorporates PVP k_{90} wherein both SR 1000 rpm appears more influential than polymer load and viscosity (Table 3). This can be explained by the weak mechanical strength of polymer chain broken by stirring effect and thus leads to small particles.

It has been reported that the loading level of polymer could have an impact on produced particle size [1]. In this study, a shift toward comparative small particle size is observed with increasing polymer load from 1% to 10% w/w which might be due to the consistent matrix formed at a higher polymer load. However, statistical analysis encourages the ignorance of such a shift (Table 3).

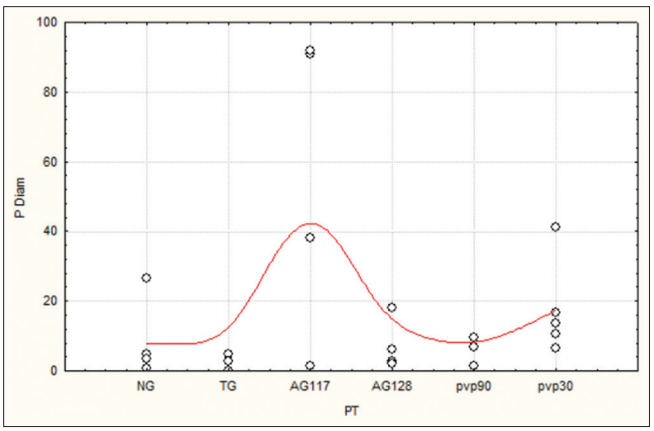

Fig. 7: Weighted least-squares fit of the relation between particles diameter and different polymers utilized as matrix agents

The influences of polymer load on particle size are prominent in R1 and R4 incorporating respective polymer loads of 1 and 10% w/w (Table 3). A proportional increase in particle size with increasing polymer load is evident, yet, statistically ignored. Such association can be explained in terms of the low viscosity emulsion formed in response to utilization of low polymer load, which offers production of small size particles irrespective of the viscosity grade of the used polymer.

Effects on measured zeta potential

For all runs with different particle sizes, zeta potential values were small (range 35.69–41.68) (Table 2) and from the statistical point as appeared in Table 3, all preparation factors have no significant effect on zeta potential. The low values can be an indication of how the CBZ is encapsulated in polymer particles and shielded in the polymer not adsorbed at the polymer surface, these findings are supported by the study [21]. Low zeta potential values are, however, associated with low stability of particles due to low electrostatic repulsive forces between the particles; consequently, the particles will have a high tendency of aggregating which, in turn, compromises the stability of the particles in a formulation [2].

On the contrary, small PDI values (close to zero) (Table 2) showed that all the samples formed monodispersions in water, a scenario which is impossible in the presence of aggregating. This suggests that the particles were stable despite the low zeta potential values. Since the three polymers have different molecular sizes, the stability could be more due to steric hindrance than surface charge [3]. Moreover, an adsorbed layer of a polymer or large molecular weight molecule tends to shift the plane of shear further from the particle surface and, as a result, the measured zeta potential decreases [24]. This means

that even in the case of highly charged particles, a relatively low zeta potential value can be recorded.

Effects on particles' EE

The reduced EE 5 observed in this study (max 52.28%) can be reasoned by the lower polymer load in the dispersed phase (1%–10%) that leads to a less viscous solution which leads to slow precipitation of the polymer at the dispersed phase surface, resulting in increased drug diffusion across the phase boundary and low entrapment. Consequently, these results are influenced by a study by Kumar *et al*. [25] which found that the encapsulation efficiency increases with increasing polymer concentration. The encapsulation efficiency increased from 53.1% to 70.9% when the concentration of the polymer increased from 20.0% to 32.5%. Yet, statistically, as shown in Table 3, the effect of polymer load on EE% is a small linear negative effect when compared to other factors with nearly zero effect. That can be interpreted by a second theory; the high viscosity and the fast solidification of the dispersed phase contributed to reducing the porosity of the microparticles as well. The authors concluded that the contribution of a high polymer load to the encapsulation efficiency can be interpreted in two ways. First, when highly concentrated, the polymer precipitates faster on the surface of the dispersed phase and prevents drug diffusion across the phase boundary. Second, the high concentration increases the viscosity of the solution and delays the drug diffusion within the polymer droplets. The last conclusion can be applied to the present result when comparing two polymer concentrations used (1% and 10%), the 1% concentration with all PTs and different SR gives a higher EE% than the 10%.

The second possible contributing factors include high polymer solubility in ethyl acetate, low ratio of the dispersed phase to continuous phase (encapsulation efficiency increases with an increase in the volume of the continuous phase), and high SR during fabrication to minimize the final particle size [22].

These findings are supported in our study as in run 1, 2, 3, 7, 8, and 9 in which the use of a high SR (1000 rpm) with low polymer load (1%) results in 52.28% EE% as in Table 3.

EE increases with decreased particle size, the highest EE% in R1, and drugs slowly diffuse inside the larger particle.

Nevertheless, the larger particle in R14 with the EE% of 45.76% indicates good incorporation of CBZ in polymer particles. That can be explained by the lower internal viscosity of gum and lower concentration in emulsion (1%) which facilitated more drug diffusion into the polymer molecule.

Effects on particles' drug load

The drug loading of the particles is generally defined as the amount of drug bound per mass of the polymer (usual moles of drug per mg polymer or mg drug per mg polymer); it could also be given as a percentage relative to the polymer [26,27].

The results of the Akbari *et al*. [3] study showed that drug loading in CBZ-loaded SLN (3:1) is 2.2 %. As mentioned above, this is because of the low solubility of CBZ in SC-CO_2. Hence, optimum drug incorporation efficiency can be tunable with an initial mass ratio of the physical mixture of drug and lipid. Fortunately, our results for drug-loaded were 5.9%–26.1% which is good results that may be due to the 1:1 drug polymer ratio, but as shown statistically in Table 3, the polymer load has small negative effects on drug loading (−0.188).

The loading process of hydrophobic drugs into the particles is thought to involve the hydrophobic interaction between the drug and the hydrophobic segment of the polymeric chains [28]. The micelles expose the polar heads of RA on the surface hampering the establishment of hydrophobic interactions with the polymer and reducing their encapsulation [1].

Effects on particles' surface morphology

SEM is giving morphological examination with direct visualization. The techniques based on electron microscopy offer several advantages in morphological and sizing analysis; however, they provide limited information about the size distribution and true population average.

The result was observed in a study by Kumar *et al*. [25] In their controlled extraction of the solvent, the solvent was removed gradually and slowly by dilution of the continuous phase, which left the microparticles in the soft state for a longer period. The resulting microparticles showed a highly porous honeycomb-like internal structure without a hollow core. That can be extended to our observation of the evaporation phase done at room temperature in a vacuuming hood for a long time which resulted in obtaining particles with different shapes and morphology as shown in Figs. 1-6.

Different PTs have shown a very predominant effect on the particle characteristics. The morphology of produced particles indicates irregular particles with hollow structures of various sizes and a thin polymer shell, either opened (arrows) or closed (deflated ball-like).

Native GG particles are irregular in shape with prismatic morphology Fig. 1, while treated GG shows different shapes and sizes of particles Fig. 2.

Whereas lower viscosity Acacia gum particles as shown in Fig. 3 have flattened structure, higher viscosity Acacia gum particles appeared more spherical and probably correlated to a modification of the elastic properties of the particles Fig. 4.

PVP K_3 particles are semi-regular ball like with hollow-core Fig. 5, and PVP K_{90} particles are hollow structures with deflated ball-like of various sizes Fig. 6.

As in the study of Grzesiak *et al*., [29] the SEM image of CBZ particles indicated that the crystal structure of CBZ has changed completely during the RESS process. CBZ has four anhydrous polymorphs. The crystal shape of polymorph I has not been identified. Polymorph II and III are, respectively, triclinic and monoclinic crystal with prismatic morphology and polymorph IV presents needle-shaped morphology. Therefore, SEM images of raw CBZ and CBZ particles show that polymorphism occurred during the RESS process due to the observed change in particles morphology in drug-loaded SLN which reveals the occurrence of coprecipitation of drug and lipid. The same finding in this study observed that the particle shape has different morphology that appears in EMS image which influenced by study stated above.

Effect on particle polydispersity

Same as in the study of Honorary *et al*. [2] suggests that the stability could be more due to steric hindrance than a surface charge. On the contrary, small PDI values (close to zero) (Table 2) showed that all the samples formed monodispersions in water, a scenario is impossible in the presence of aggregating. This suggests that since the three polymers have different molecular sizes, the stability could be more due to steric hindrance than surface charge [2].

Native GG was used in Runs (1, 4, 13, and 16) as in Table 2, the smallest particles produced in R1 (769.81) with high polydispersity (5.487) were explained by the higher internal viscosity of the polymer that led to increased particle aggregate in solution and decreased stability in storage.

The high polydispersity in R 17 (1.093) can be explained by its large particle (91,830.82) as stated in the study of Honary *et al*. [2]. The samples of acacia gum result indicates that bigger particles are more rapidly trapped by the high voltage collection system than smaller ones, this phenomenon is further intensified by the surface charge density of the macromolecules.

However, when we go through the other Acacia gum lower and high viscosity runs, we find that there is a very weak relationship between the particle size and the PDI. This is attributed to the specific surface-active features of the acacia gum and its affinities with the oily components of the emulsion, which can induce droplet flocculation and destruction [2].

CONCLUSION

In this study, the technique used in producing nanoparticles has an abundant effect on its character but not more than the PT which plays a key role in all the steps.

The main goal of this research evaluation of the GG, acacia gum, and polyvinylpyrrolidone, each of two grades, for use as crosslinker in nanotechnology, was done from a different point of view, and it was founded that Acacia gum has the more interesting properties in developing submicron particles.

RECOMMENDATION

Different polymers need special techniques in producing crosslinked particles with sub-micron particles no universal technique can be applied.

The source of GG should be unified to get the same reference results of treatment.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest, except that publication of this article will advance their CV.

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APPENDIX

Constraints and multi-linear regression equations for prediction of a composite index for different natural gum linkers based carbamazepine tableted nanoparticles.

Polydispersity index (PDI%), (Range: 0.1–0.45; ideal: 0.28)

- For below ideal
  - Observed – Transformed
  - 0.1=0
  - 0.28=.33
  - Transformed=1.8333*Observed–0.1833

- For above ideal
  - Observed–Transformed
  - 0.28=0.33
  - 0.45=0
  - Transformed=0.8735–1.9412*Observed

Entrapment efficiency (EE%) (range: 40–100; ideal: 70%)

- For below ideal
  - Observed – Transformed
  - 40%=0
  - 70%=0.33
  - Transformed=1.1*Observed–0.44

- For above ideal
  - Observed – Transformed
  - 70%=0.33
  - 100%=0
  - Transformed=1.1–1.1*Observed.