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Evaluation and Ranking of Drug Release from Different Grades of Guar Gum, Acacia Gum and Polyvinyl Pyrrolidone as Cross-Linkers in Submicron Particles

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Objective: The main goal of this research is to Improve Carbamazepine water solubility and drug release properties by nano sizing, and using guar gum, Acacia Gum and poly-vinylpyrrolidone, each of two viscosity grades, as crosslinking agents. Moreover, the study is extrapolated, utilizing composite index (CI) design and mathematical modelling, in an attempt to locate the most suitable set of the factors that affect nanoparticles produced with optimum specifications.

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Objective: The main goal of this research is to Improve Carbamazepine water solubility and drug release properties by nano sizing, and using guar gum, Acacia Gum and poly-vinylpyrrolidone, each of two viscosity grades, as crosslinking agents. Moreover, the study is extrapolated, utilizing composite index (CI) design and mathematical modelling, in an attempt to locate the most suitable set of the factors that affect nanoparticles produced with optimum specifications.

Methods: The method used nano and submicron particles that were produced in our previous study (Evaluation of different grades of guar gum, acacia gum and polyvinyl pyrrolidone as cross-linkers in producing submicron particles). All runs were subjected to drug release investigations according to which a weighted composite index was generated.

Results: Based on the obtained findings and the associated statistical analysis, particles of run8 were found to be the best ranked as they fulfilled all the constraints.

Conclusion: Acacia gum was found to have the most interesting properties in developing submicron particles with controlled drug release, accordingly the study recommends the need for further investigations.

Keywords: polymer, Guar gum, acacia gum, polyvinyl pyrrolidine, carbamazepine, drug release, composite index.

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I. Introduction

a) Drug Release

A central reason for pursuing nanotechnology is to deliver drugs, hence understanding the manner and extent to which the drug molecules are released is important. The drug loading of the nanoparticles is generally defined as the amount of drug bound per polymer mass (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.

Nanoparticles made of polysaccharides, due to their unique properties, are promising carriers to deliver and protect the physiological properties of hydrophilic drugs and have been successfully applied as drug delivery systems (1) As natural biomaterials, polysaccharides are stable, safe, nontoxic, hydrophilic, and biodegradable.

b) Biological benefits of nanoparticles

The property of nanoparticle formulations that make this approach highly beneficial is related to the surface properties imparted on nanometer-sized entities (2). Applying Nano-crystal Technology or one of the alternate nanoparticle formulation approaches to the many formulation and performance issues associated with poorly water-soluble compounds in the pharmaceutical industry provides many benefits.

c) The Solubility Challenge

It is estimated that ~40% of active substances identified through combinatorial screening programs are difficult to formulate as a result of their lack of significant solubility in water (3, 4, and 5). In one sense, this is understandable. If a molecule must penetrate a biological membrane to be absorbed, the molecule generally must possess some hydrophobic or lipophilic characteristics. When these types of situations arise, a nanoparticle formulation approach has proven to be very useful and invaluable in all stages of drug development and has opened opportunities for revitalizing marketed products with suboptimal delivery.

d) Guar gum

Guar gum (GG) is galactomannan derived from Guar *Cyamopsis tetragonolobuskernels* which belong to family *Leguminosae.*

It is biocompatible, biodegradable, non-toxic, low-cost and amenable to chemical modifications, properties that make it an ideal material for developing drug delivery formulations (6). However, native guar gum has also shortcomings such as, uncontrolled rates of hydration, high swelling, thickening effect, instability upon storage, high susceptibility to microbial attack and the difficulty to control viscosity due to relative fast biodegradation (7).

Thermal treatment of guar gum at 70℃ for 10 minutes is an efficient tool to produce guar gum with desired properties for pharmaceutical processing and industries. The treatment has resulted in the production of treated guar gum 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 resultant treated guar powder and verification of such effect might necessitate a more collaborated extended study (8).

e) Acacia Gum

This is the dried exudate of the acacia tree (*Acacia senegal*or related species of *Acacia* Fam. *Leguminosae*. The gum is highly soluble in water. Physically, acacia is considered to be a complex, highly branched, globular molecule, which is closely packed rather than linear, thus accounting for its low viscosity. Rheologically, acacia gum solutions exhibit typical Newtonian behavior at concentrations up to 40%. Above 40%, solutions become pseudoplastic, as is shown by a decrease in viscosity with increasing shearing stress (9).

f) Povidone

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 (10, 11), Due to its hydrophilicity and rapid dissolution in an aqueous medium, PVP is very frequently applied as a carrier in immediate release dosage forms. PVP has a long history of use in human drug products and high molecular weight PVPs generally do not get absorbed in the GI tract.

g) Carbamazepine (*CBZ*)

One of the bad soluble active drug substances. Although Carbamazepinehas a high intestinal permeability, its bioavailability is limited by its low water solubility (0.11mgmL−1) (2).

5H-ibenz[b,f]azepine-5-carboxamide A white or almost white crystalline powder. It exhibits polymorphism that is very slightly soluble in water; sparingly soluble in alcohol and in acetone, and freely soluble in dichloromethane.

Carbamazepine is widely distributed throughout the body and is about 70 to 80% bound to plasma proteins. It induces its own metabolism so that the plasma half-life may be considerably reduced after repeated dosage.

The mean plasma half-life of carbamazepine on repeated dosage is about 12 to 24 hours; it appears to be considerably shorter in children than in adults.

Carbamazepine is a dibenzazepine derivative with antiepileptic and psychotropic properties. It is used to control secondarily generalisedtonic-clonic seizures and partial seizures and in some primary generalized seizures.

h) Composite index

A composite index is a grouping of equities, indexes or other factors combined in a standardized way, providing a useful statistical measure of overall market or sector performance over time, and it is also known simply as a "composite." Usually, a composite index has a large number of factors that are averaged together to form a product representative of an overall market or sector (12).

II. Materials and Methods

Materials: The Nano and submicron particles produced in our previous study (Evaluation of different grades of guar gum, acacia gum and polyvinyl pyrrolidone as cross-linkers in producing submicron particles) as in Table1 are used in this study

Table I: Layout of formulation runs according to mixed 3-2 -levels factors and 1- 3-levels factor statistical design

Run	Stirring Rate	Polymer grade	Polymer load	Polymer type
R1	1000	G-non treated	1%	Guar gum
R2	1000	Acacia lower viscosity	1%	Acacia Gum
R3	1000	Povidone K90 higher viscosity	1%	Povidone
R4	1000	G-non treated	10%	Guar gum
R5	1000	Acacia lower viscosity	10%	Acacia Gum
R6	1000	Povidone K90 higher viscosity	10%	Povidone
R7	1000	G- treated	1%	Guar gum
R8	1000	Acacia higher viscosity	1%	Acacia Gum

R9	1000	PovidoneK30 lower viscosity	1%	Povidone
R10	1000	G- treated	10%	Guar gum
R11	1000	Acacia higher viscosity	10%	Acacia Gum
R12	1000	PovidoneK30 lower viscosity	10%	Povidone
R13	500	G-non treated	1%	Guar gum
R14	500	Acacia lower viscosity	1%	Acacia Gum
R15	500	PovidoneK30 lower viscosity	1%	Povidone
R16	500	G-non treated	10%	Guar gum
R17	500	Acacia lower viscosity	10%	Acacia Gum
R18	500	PovidoneK90 higher viscosity	-10%	Povidone
R19	500	G- treated	1%	Guar gum
R20	500	Acacia higher viscosity	1%	Acacia Gum
R21	500	PovidoneK30 lower viscosity	1%	Povidone
R22	500	G- treated	10%	Guar gum
R23	500	Acacia higher viscosity	10%	Acacia Gum
R24	500	PovidoneK30 lower viscosity	10%	Povidone

a) Apparatus

The following instruments were used in the experimental part of this study:

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

b) Methods

Collected submicron particles from all runs were subjected to the following qualifications.

c) Particle size analysis

By using particle size analyser 90, measurements of polydispersity (PD %) 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.

d) Entrapments efficiency of nanoparticles

Dried nanoparticles were dissolved in ethyl acetate (a common solvent for polymers and drug samples). The amount of entrapped carbamazepine that was present in the solution was measured spectrophotometrically at 287 nm (USP, 13).

Drug incorporation efficiency was expressed both as Drug Content (% w/w), also referred to as drug loading in the literature, and Drug Entrapment (%); represented by Eqs. (1) and (2) respectively. The individual values for two replicate determinations and their mean values were reported

$$\text{Drug loading (\% w/w)} = \frac{Mass\ of\ drug\ in\ nanoparticles}{Mass\ of\ nanoparticle}\%100 \quad (1)$$

$$\text{Drug Entrapment (\%)} = \frac{Mass\ of\ drug\ in\ nanoparticles}{Mass\ of\ drug\ used\ in\ formulation}\%100 \quad (2)$$

e) Nanoparticle drug release assessment

All runs were subjected to drug release investigations where the amount of particles equivalent to 1 g of carbamazepine was weighed and transferred to a dissolution test beaker containing 1L of sodium lauryl sulphate. 3ml of each sample was filtered into 100 ml volumetric flask and the absorbance of the samples was determined at 287 nm against water as a blank (14). Making use of the drug calibration curve (as discussed next), the amount of carbamazepine was then estimated. The assay method was derived from the USP carbamazepine tablets dissolution test monograph (USP, 13).

f) Calibration curve

From the reference standard Carbamazepine, 40 mg was accurately weighed and dissolved in 8 ml absolute methanol, 1 ml of this solution was taken and diluted to 10 ml. Serial dilutions were then carried out to obtain solutions of different drug concentrations. The absorbance of each concentration at 287nm was determined spectrophotometrically and a calibration curve was thus generated (USP,13).

g) Composite index design

A weighted composite index was generated for the data to designate a single score utilizing three constraints (15). This was done in order to select the optimized factors setting (polydispersity, Entrapment Efficiency and nanoparticle drug release rate at 60 mints) that could possibly yield the most desired properties for drug granules and tablets. The process of statistical composite index application was aided by the computer Excels program.

III. Results

a) Characterization of produced particles

Table 2 summarizes the polydispersity index (PDI %) and entrapment efficiency (EE %) properties of produced particles within different formulation runs. The Carbamazepine calibration curve and drug release profiles of different formulation runs are depicted in figures 1 and 2, respectively.

Table 2: Polydisperse index (PDI %) and entrapment efficiency (EE %) of yielded particles within different formulation run

Run No.	EE	PDI
R1	52.3%	5.50%
R2	52.3%	0.52%
R3	52.3%	1.76%
R4	13.1%	0.37%
R5	13.1%	0.50%
R6	13.1%	0.43%
R7	52.3%	0.62%
R8	52.3%	0.30%
R9	52.3%	0.67%
R10	13.1%	0.39%
R11	12.5%	4.04%
R12	11.8%	0.40%
R13	39.6%	0.55%
R14	47.0%	0.44%
R15	45.0%	0.69%
R16	12.7%	0.38%
R17	13.1%	1.09%
R18	13.1%	1.04%
R19	52.3%	0.09%
R20	52.3%	0.38%
R21	52.3%	0.56%
R22	13.1%	1.74%
R23	13.1%	0.81%
R24	13.1%	16.64

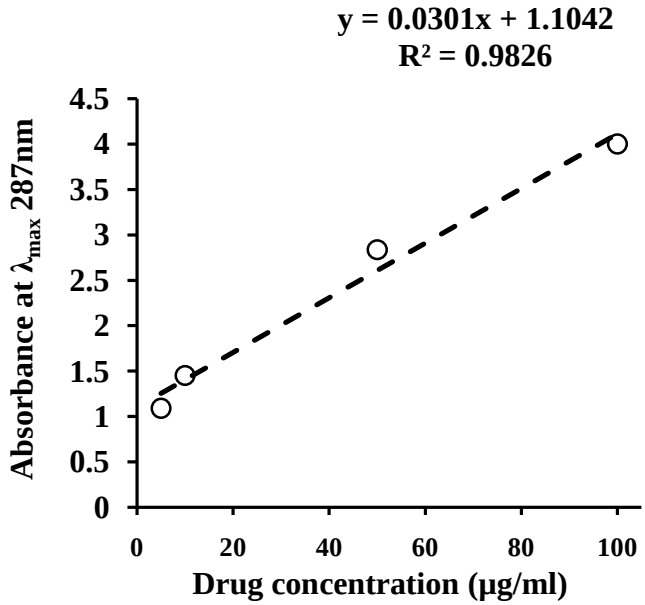

Fig. 1: Calibration plot for determination of Carbamzepine in solutions using UV method. Each data point is the average of 3 determinations, R^2: correlation coefficient

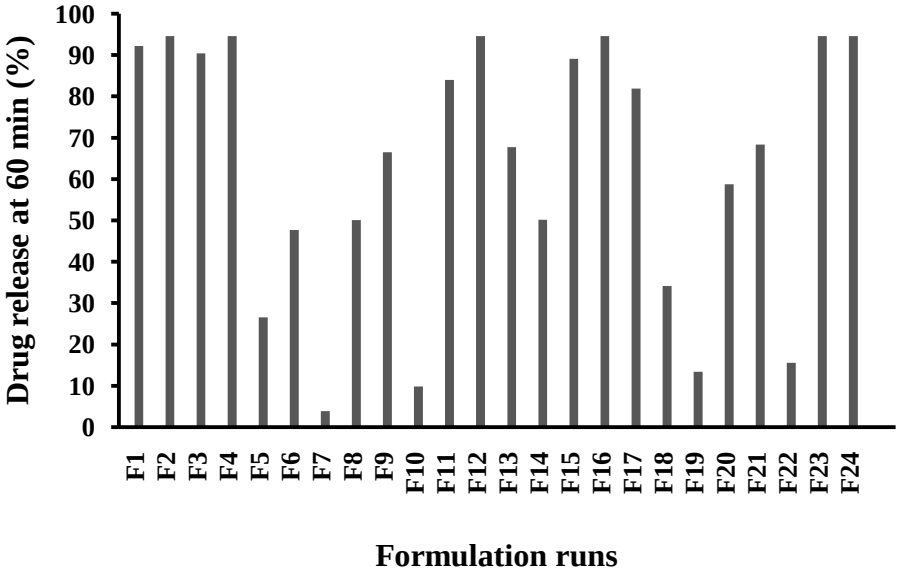

Fig. 2: Cumulative % drug released after 60 Min. of particles within different formulation runs

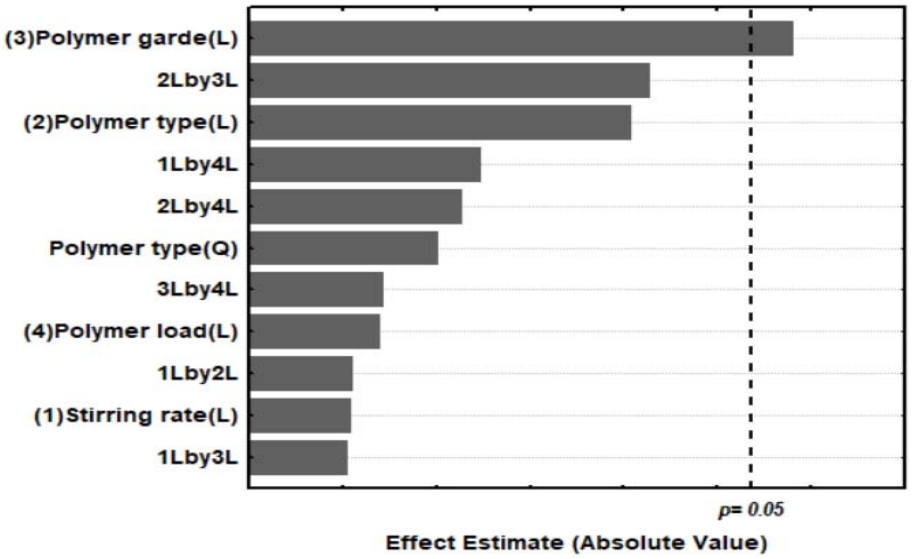

Fig. 3: Estimated effects of the linear (L) and quadratic (Q) and joined influences of the investigated variables on percent drug release at 60 min of different formulations within the experimental design where p= 0.05 denotes cut-off point for significant influences

Composite index scoring and ranking of different formulations of carbamazepine-loaded polymeric particles

Table 3 abridges the composite index scoring and the subsequent ranking of different formulations in the design based on preset of selected 3 constraints of polydispersity index (PDI), entrapment efficiency (EE %) and drug release at 60 min (% $Rel_{60\ min}$).

Table 3: Composite index (CI) and subsequent ranking order of different formulations in the design based on pre-set constraints for particles polydispersity index (PDI %), entrapment efficiency (EE %) and drug release at 60 min (%Rel_{60min})

Run No.	Responses values			Transformed responses			CI	Ranking
	PDI %	EE %	%Rel_{60min}	PDI %	EE %	%Rel_{60min}		
R1	5.50	52.3	70	0	0.14	0	0.14	7
R2	0.52	52.3	73	0	0.14	0.07	0.21	4
R3	1.76	52.3	68	0	0.14	0	0.14	7
R4	0.37	13.1	73	0.16	0	0.07	0.23	3
R5	0.50	13.1	15	0	0	0	0.00	13
R6	0.43	13.1	26	0.04	0	0	0.04	12
R7	0.62	52.3	5	0	0.14	0	0.14	7
R8	0.30	52.3	28	**0.29**	**0.14**	0	**0.43**	**1**
R9	0.67	52.3	45	0	0.14	0	0.14	7
R10	0.39	13.1	6	0.12	0	0	0.12	8
R11	4.04	12.5	62	0	0	0	0.00	13
R12	0.40	11.8	73	0.10	0	0.07	0.17	6
R13	0.55	39.6	46	0	0	0	0.00	13
R14	0.44	47.0	28	0.02	0.08	0	0.10	9
R15	0.69	45.0	67	0	0.06	0	0.06	11
R16	0.38	12.7	73	0.14	0	0.07	0.21	5
R17	1.09	13.1	60	0	0	0	0.00	13
R18	1.04	13.1	12	0	0	0	0.00	13
R19	0.09	52.3	8	0	0.14	0	0.14	7
R20	0.38	52.3	37	0.14	0.14	0	0.28	2
R21	0.56	52.3	46	0	0.14	0	0.14	7
R22	1.74	13.1	9	0	0	0	0.00	13
R23	0.81	13.1	73	0	0	0.07	0.07	10
R24	0.54	13.1	73	0	0	0.07	0.07	10

IV. Discussion

a) Drug release Studies

A central reason for pursuing nanotechnology is to enhance drug delivery, hence understanding the manner and extent to which the drug molecules are released is important. In order to obtain such information most release methods require that the drug and its delivery vehicle be separated (16, 17).

For the drug to be released from the Polymer particles, the Polymer undergoes degradation by hydrolysis or biodegradation through cleavage of its backbone ester linkage into oligomers and finally monomers (18).

b) Calibration curve of standard carbamazepine

The generated calibration curve for standard CBZ in solutions using the validated UV assay method shows high acceptable linear correlation regression between drug concentration and UV absorbance with a highly established correlation coefficient ($R^2 = 0.9826$) in the drug concentration range of 1—100μg/ml (Fig. 1).

c) Effects on drug release characteristics

The effect of different variables on drug release at 60min for different formulations has been studied. Fig 3, showed the linear, quadratic and joined influences of polymer type, polymer grade, polymer load and stirring rate. Among the different variables investigated, the polymer grade has the predominant and significant effect on drug release over the other variables, it has a linear effect with $p > 0.05$ which is the cutoff point. Polymer type (2) has less effect than the polymer grade(3) and when joining their linear effect (2 and3) it appears less than (2) and more than (3). Only the polymer type has a quadratic effect on drug release but it was a non-significant one.

d) Relation between polymer (type, grade) and drug release

Similar to what was found in a study done by Nur et al (19) considering Guar gum, Treated Guar Gum, and Xanthan Gum, as drug fabricating polymers, different drug release profiles were also present in this study. This might be related to their dissimilar hydration and swelling attributes that determine the rate at which the surface viscous barrier (controlling gel) is being formed. These findings along with the effect of particle size and EE% can explain the variation in CBZ release profile from the different gums. Moreover, the statistical work shown in fig 3 reveals the predominated effect of polymer grade (viscosity) as a significant effect over the other factors. Following is a discussion on the effect of different polymer grades on CBZ release.

Considering Native Guar gum, a fast release of 20% to 40% was observed immediately after the addition of loaded particles. This doesn't go along with Nur et al study and it's likely due to a fraction of CBZ present on the surface of the particles being immediately released upon coming in contact with the SLS medium.

However, native guar gum has also shortcomings such as uncontrolled rates of hydration, high swelling, thickening effect, instability upon storage, high susceptibility to microbial attack and the difficulty to control viscosity due to relative fast biodegradation (20). Various strategies were developed in order to overcome these issues, offering the opportunity to tailor the physical and chemical properties of guar gum thus yielding materials that may find a wide range of applications

Regarding Treated Guar gum, the CBZ release was found to be delayed. Less than 30% of the drug entrapped was released within 120 Min., This goes parallel with the results of Nur et al (21), which reported low hydration and swelling capabilities of the treated gum. Accordingly, this is reflected in the enhancement of drug release as a result of the delay in the formation of the gel layer that controls the drug release. Such a result is a good explanation of the poor release profile from the treated guar as for the particle in order to release the entrapped drug, the particle must be swollen to permit the drug release.

In Povidone K_{30} (Lower viscosity) the fastest and uniform release was shown with polymer concentration 1% (R 9 &R21) which has higher EE%. This can be explained by the lower viscosity of the prepared emulsion producing small particles and the high hydrophilicity of povidonek30. All these parameters can increase drug dissolution, which is reported by a study published in ISP Pharmaceuticals (11). The study used low molecular weight PVPs as carriers in solid dispersions due to their higher aqueous solubility, lower viscosity in the diffusion boundary layer, and faster dissolution rate. the study revealed that solid dispersions of indomethacin from co-precipitation and spray drying processes showed faster release from PVP with low molecular weight (PVP K30) than those with high molecular weight (PVP K90) (22).

In our study, the release of CBZ from PVP K30 was very fast in R24. This is can be due to the lower EE% which means that the drug is on the surface of particles not entrapped due to the emulsion's high viscosity as a consequence of increased polymer concentration (10%). This high viscosity renders the drug from diffusing into a polymer molecule and crosslinking with it.

Another study, done by Bharali et al (23), investigated the characteristics of in vitro release of entrapped PVP at low loadings of the compound, which remains in the form of a molecular dispersion inside PVP particles. It was found that when the concentration of dye inside the core of the particle is very high, a part of it is associated or clustered, which has to be dissolved and released more slowly out of the particles. These

phenomena appear clearly in our study in R 21 which has a higher EE% of 52% with a lower release rate.

Regarding Povidone k90 (High viscosity) High molecular weight grade PVP K90 dissolves in a large variety of organic solvents. However, due to its hydrophilicity, its moisture uptake level is high (24) which may result in difficulties in its physical stability leading to drug crystallization in the carrier polymer caused by the plasticizing effect of absorbed water.

The drug release profile of the four runs (3,6,15,18) is strongly linked with EE% as increase EE% increase drug release, R 3 and R15 reached 90% release in 60 minutes as shown in Table 4. The fastest one is in R15 (76% release at 30 mins) can be attributed to the amount of CBZ entrapped (less than 50%) and hence more drugs are on the particle surface leading to burst release (more than 30% in the first 10 mints) (25)

With respect to Lower viscosity, Acacia gum showed the slowest release rate among runs, higher viscosity of acacia, large particle and higher polydispersity as seen in Table2 are the responsible factors. R2 small particle and high EE% these results are not in accordance with relevant published work discussed above. As EE% is a result of how a drug is cross-linked with a polymer, a decreased viscosity will lead to an increase in EE% as less barrier is present, this was seen in R2 (1%polymer concentration produces a solution of lower viscosity) even with large particle sizeR5 with smaller particles (1433.38) than R2 though with lower EE% can be explained the same way.

Considering the higher viscosity of acacia gum runs, a fast release profile was observed which can be relied on for the burst release. More than 20% to 47% of drugs are released in the first 10 minutes with lower EE%, which means the drug is on the particle surface and not entrapped as seen in R 11 and R 23 with less EE%.

In R 8 and R 20 the EE% is high; it has a fast release of 20 % this can be explained by their small particle increasing drug solubility and accordingly enhancing drug release

e) Effect of particle size on drug release

Particle size distribution and morphology are the most important parameters of the characterization of particles. In a study done by (25), it has been found that particle size affects drug release. Smaller particles offer a larger surface area. As a result, most of the drug-loaded onto them will be exposed to the particle surface leading to fast drug release, despite these findings present study found that the smallest particle of R19 (131.72) and R22 (168.25) have the slowest drug release. This may be contributed to the nature of treated guar gum used, thermal treatment of guar gum lead to new gum with odd properties due to degradation of the polymer chain. On the contrary, R1 (native guar) which has a particle size (769.81) showed fast drug release (41.83%) in the first 10 minutes, which support the finding of Robinson (11). Such results can give us a good indication that drug release is mainly affected by polymer characteristics rather than particle size. When we go through the runs we find that R 5 & R 3 have almost the same particle size (1.43 & 1.45) but with different drug releases. R5 (lower viscosity Acacia gum) have 18.83% of drug released in the first 10 minutes while R 3 (povidone lower viscosity) has 45.48% of drug released in the first 10 minutes which support the above finding as seen in Table 4.

Polymer degradation can also be affected by particle size. For instance, the degradation rate of poly (lactic-co-glycolic acid) was found to increase with increasing particle size in vitro (26).

f) Relation between EE% and drug release

The fast drug release in first 10 minutes can be explained by the EE%, as the drug on surface of the particle is released before the entrapped one. This finding appear in R 16 and R 4 (native Guar) with large particle size (3,600.58 &26,450.88) and drug release 34.12% &50.20% respectively

It also ppear in povidone k90 R 12 and R 24 (release 33.66% & EE% 11.49%) (Maximum release 67.02% and EE% 12.88%), respectively (Table 4).

A fast release of 20% to 40% was observed for native guar run just after the addition of loaded particles, likely due to a fraction of CBZ present on the surface of the particles being immediately released in contact with the simulated fluids. The CBZ released in the SLS medium over the total duration of the experiment reached 85 %, indicating that the release of CBZ from the particles can also be controlled by pH.

g) Optimization by composite indexing

Using composite index design as ranking tool prove to be effective in evaluating each factor in an equal way that help in making decision with strong statistical view.

Since the relative contribution of each individual constraint to the true composite score within each step was unknown, the decision was made to assign an arbitrary value of 1/3 to each of the three factors and, accordingly, each test result was transformed to a value between 0 and 0.33. Within each separate step, multi-linear regression equations were applied for the three constraints in order to generate the composite index (CI) for each selected constraint including higher than and lower than ideal values. The run having the highest composite index would be considered as a batch fulfilling the constraints and consequently would be considered as an optimized one.

Table 3 abridged the composite index scoring and the subsequent ranking of the different 24 runs based on the previously mentioned preset 3 constraints of (EE%, PDI and R% at 60 mints) in composite index are summarized in Table 3,

The generated composite index scoring for Runs in this series has ranked R 8 as first run though it has R% 28 at 60 min with increased EE% and the smallest PDI(0.3) lead to increase its efficiency in rank

V. Conclusion

It was found that Acacia gum has the more interesting properties in developing submicron particles like controlling drug release, and hence need to be studied further, while polymer viscosity has large impact on particles behavior.

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