

PHARMACEUTICAL RESEARCH

Preliminary Evaluation of Glipizide Spheres and Compacts from Spheres Prepared by Cross-Linking Technique

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The objective of this research was to use the natural polymer Carrageenan to obtain controlled release spheres loaded with glipizide using the cross-linking technique. The effect of polymer level and drug load were investigated. The drug was dispersed in Carrageenan solution and the dispersion was dropped by a device containing 3 disposable syringes into cross-linking solution containing 3% calcium chloride. After 15 minutes residence time, the spheres were collected by decantation and dried in hot air oven at $38^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for 24 hours. The dried spheres were successfully compacted into tablets using rotary Manesty B-3B machine equipped with 12/32 inches round flat face punches, target tablet

weight was $400 \text{ mg} \pm 5\%$. As the polymer level was increased in the sphere formulation, the drug release rate was increased. However, as the drug level was increased in the sphere formulation, the release rate was decreased. This trend was also true for tablets compacted from spheres. The scanning electron microscope photographs supported the dissolution data. More cracks and rough surface were observed in tablets compacted from spheres containing high polymer level and low drug level.

Key Words: Cross linking technique, Glipizide, Spheres; Compacted spheres, Carrageenan, pellets.

Spherical pellets for pharmaceutical uses are of interest for both conventional dosage forms and controlled release delivery systems. In past years, considerable attention has been focused on the development of spherical pellets (1-3). Among their characteristics are the particle shape and size distribution which are important factors in flow. Spherical particles led to lower angles of repose and higher bulk densities. These effects should result in better flow properties, smaller tablet weight variation, and more efficient compressibility characteristics (4).

Different techniques can be used to obtain spherical particles (5-7). Cross-linking method is one of the technique that can be used to obtain spherical particles. Cross-linking has been defined as the union of two chains of polymer molecules by bridge composed of either an element, a group, or a compound that join certain atoms of the chains by primary bonds. It can be achieved by addi-

tion of chemical substance (cross-linking agent) and / or exposing the polymer to heat or high energy radiation (8).

Natural polymers have been extensively evaluated for pharmaceutical application controlled drug delivery dosage forms, specially for use in bead preparation (9), as a gel matrix for immobilization of proteins (10-11) and as a sustained release spheres (12).

Carrageenan is a water soluble hydrocolloid obtained by extraction with water or aqueous alkali, from some species of the red seaweeds. Carrageenan is commercially used as thickening, suspending and gelling agents (13 14).

Limited studies have been reported for the use of Carrageenan in controlled release systems (15-17). This is the first research related to evaluation of glipizide spheres using carrageenan and compacts from spheres prepared by cross linking technique. The effect of factors such as drug level and polymer level on physical properties of the spheres and on drug release were investigated. Additionally, the drug release from spheres and compacted spheres were evaluated.

Materials

Except when noted, all chemicals were analytical grade and used as received. Glipizide, lot number 58P902-07000, was selected as the model drug and was supplied by Pfizer,

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Inc. (Puerto Rico); Carrageenan, lot number ZB502 (Gelcarin, GP 8120) was supplied by FMC Corp. (Marine Colloid Division, Newark, DE).

Methods

Preparation of suspension. Five formulations were prepared and the batch size for each formulation was 500 ml. In the first three formulations, the level of drug was held constant at 6% w/v and the level of Carrageenan varied, 2% w/v, 3% w/v and 4% w/v. For the last two formulations, the level of Carrageenan was held constant at 3% w/v and the level of glipizide varied, 3% w/v and 9% w/v.

Carrageenan solutions were prepared by adding while stirring, the polymer to 350 ml distilled water previously heated to 60°C-65°C. The drug was added while stirring to the Carrageenan solution. Stirring continue until homogenous suspension was obtained.

Sphere formation. The suspension (60°C-65°C) was dropped from a device composed of three syringes each filled with 25 ml homogeneous suspension, at a rate of 4.5 ml/minute into a beaker containing 100 ml of 3% w/v calcium chloride cross linking solution.

The agglomeration occurred instantaneously and every drop turned into sphere, strong enough to withstand handling. The residence time of the spheres in the cross-linking solution was 15 minutes, after which the spheres were collected by decantation from the cross-linking solution.

Bulk and tapped density. Samples of 25 g each were evaluated for bulk and tapped density (g/ml) in duplicate. For bulk density determination, each sample was poured into a 100 ml graduated cylinder using a large funnel and the volume occupied was measured. The weight was divided by the bulk volume to obtain bulk density.

The tapped density was determined by Vanderkamp tap density tester. The sample was poured into a 100 ml measuring cylinder, placed in a tester, and tapped 100 times. In order to obtain tapped density, the weight of the sample was divided by the tapped volume (volume occupied after tapping in milliliters).

Particle size of spheres. The diameter of 10 spheres from each formulation was determined using a caliber. The mean diameter and standard deviation were calculated.

Compaction of spheres. Spheres were compacted into tablets using rotary Manesty B-3B machine equipped with 12/32 inches round flat face tooling. Target tablet weight was 400 mg +5% and target hardness was 7-9 Kp.

Friability. Erweka friabilator fitted with an abrasion wheel was used for measurement of friability of spheres.

A 10 g sample of spheres was introduced in the friabilator and processed at 250 rpm. For tablets, 5 tablets was introduced in tablet friabilator and was processed at 100 rpm. The percent friability was calculated using the following formula:

$$\text{Percent friability} = \frac{(\text{initial weight} - \text{final weight})}{\text{initial weight}} \times 100$$

Scanning electron microscope. The scanning electron microscope was used to study the surface morphology of the spheres and compacts. The samples were mounted in Auto sputter Coater (Biorad ES200) and covered with gold. Magnification used was 20X.

Disintegration time. A total of six tablets were tested separately for disintegration (Erweka disintegration apparatus). The test was performed using 900 ml distilled water maintained at 37 +2°C as the immersion fluid. The disintegration time for each tablet was recorded and the mean was calculated.

Drug content. Pulverized spheres (400 mg) was introduced in 1000 ml volumetric flask, completed to volume with phosphate buffer pH 7.4 and stirred for 4 hours using magnetic stirrer. The solution was filtered and the amount of drug per 400 mg spheres was determined from the absorbance at 276 nm using U.V. spectrophotometer.

Dissolution testing. The dissolution of glipizide from all tablets compacted from spheres was measured in 900 ml phosphate buffer pH 7.4 at 37 + 0.5°C using rotating basket apparatus (Hanson Research, Model SR2) at a speed of 50 rpm. Filtered samples were withdrawn and assayed for drug concentration using U.V. spectrophotometer (Bechman Instruments, Model DU-65) at 276 nm. The number of replicates for each formula was 3.

Results and Discussion

Spheres and compacts from spheres were successfully prepared from all formulations. Table 1 shows the drug content in the sphere formulations.

Bulk density for spheres prepared with 6% w/v glipizide and different Carrageenan level (2% w/v, 3% w/v and 4% w/v) varied from 0.26-0.28 g/ml (Table 2).

Table 1. Drug Content for Sphere Formulations Prepared by Cross Linking Technique (mg glipizide/400 mg spheres)

Spheres containing 6% w/v glipizide and different Carrageenan levels (% w/v)	Spheres containing 3% w/v Carrageenan and different glipizide levels (% w/v)					
	2	3	4	3	6	9
	110.23 mg	114.5 mg	120.3 mg	56.7 mg	114.5 mg	154.9 mg

Spheres prepared with 6% w/v glipizide and 2% w/v Carrageenan gave highest bulk density (0.28 g/ml). The tapped density (1000 taps) for spheres of the same composition varied from 0.22-0.25 g/ml. Spheres prepared with 6% w/v glipizide and 2% w/v Carrageenan gave highest tapped density (0.25 g/ml). In general as the polymer increased in the spheres, the bulk and tapped density of the spheres decreased.

Bulk density for spheres prepared with 3% w/v Carrageenan and different glipizide level (3% w/v, 6% w/v and 9% w/v) varied from 0.25 – 0.29 g/ml (Table 2). Spheres prepared with 3% w/v Carrageenan and 3% w/v glipizide gave highest bulk density (0.29 g/ml). Tapped density (1000 taps) for spheres prepared with 3% w/v Carrageenan and different glipizide level varied from 0.23-0.27 g/ml. Spheres prepared with 3% w/v Carrageenan and 3% w/v glipizide gave the highest tapped density (Table 2). The same results were true. As the drug level increased in the spheres, the bulk and tapped density decreased.

Table 2 shows the mean particle diameter for all sphere formulations. The mean particle diameter for spheres

Table 2. Effects of Glipizide Levels, and Carrageenan Levels on the Physical Properties of Glipizide Spheres

Physical properties	Spheres containing 6% w/v glipizide and different Carrageenan levels (% w/v)			Spheres containing 3% w/v Carrageenan and different glipizide levels (% w/v)		
	2	3	4	3	6	9
Bulk density, g/ml (n=3)	0.28	0.27	0.26	0.29	0.27	0.25
Tapped density, g/ml (n=3)	0.25	0.24	0.23	0.27	0.24	0.23
Mean particle diameter (n=20)	1.43	1.56	2.24	1.26	1.56	2.74
Mean friability percent (n=3)	0.81	0.63	0.56	0.71	0.63	0.05

prepared with 6% w/v glipizide and 2% w/v Carrageenan was 1.43 mm while the mean particle diameter for spheres of the same composition but prepared with 3% w/v and 4% w/v Carrageenan was 1.56 mm and 2.24 mm respectively. As the percent of polymer was increased in the formula, the diameter of the spheres was increased. Spheres prepared with 3% w/v Carrageenan and different glipizide level (3% w/v, 6% w/v and 9% w/v), their mean particle diameter varied from 1.26 mm to 2.74 mm. As the drug level increased in the spheres, the diameter of the spheres increased. The friability percent for spheres prepared with 6% w/v glipizide and different Carrageenan level varied

from 0.56 to 0.81%. Spheres prepared with 6% w/v glipizide and 4% w/v Carrageenan were very hard and gave lowest percent friability (0.56%). As the level of polymer increased in the spheres, percent friability decreased. The friability percent for spheres prepared with 3% Carrageenan and different glipizide level (3% w/v, 6% w/v and 9% w/v) varied from 0.05 to 0.71%. The friability percent for spheres prepared with 3% Carrageenan and 9% glipizide was 0.05% (Table 2). The same results were true for the level of drug in the spheres. As the level of drug increased, the friability of the spheres decreased.

Figure 1 shows the scanning electron photomicrographs for spheres prepared with 6% w/v drug and 2% polymer (Figure 1-a), spheres prepared with 6% w/v drug and 4% w/v polymer (Figure 1-b), spheres prepared with 3% w/v polymer and 3% w/v drug (Figure 1-c) and spheres prepared with 3% w/v polymer and 9% w/v drug (Figure 1-d). No difference in the surface morphology was observed between spheres prepared with 6% w/v drug and different polymer level. However, porosity on the surface of spheres prepared with constant level of Carrageenan (3% w/v) and different levels of glipizide appears to be decreased as the level of drug was increased in the formula. The magnification is 20X.

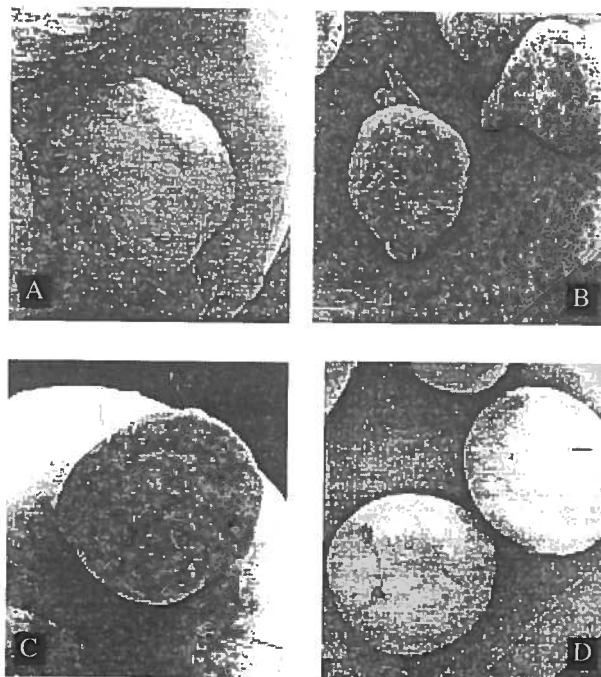


Figure 1. Scanning electron photographs for spheres prepared with 6% w/v glipizide and 2% w/v Carrageenan (1-a), spheres prepared with 6% w/v glipizide and 4% w/v Carrageenan (1-b), spheres prepared with 3% w/v Carrageenan and 3% w/v glipizide (1-c), and spheres prepared with 3% w/v Carrageenan and 9% w/v glipizide (1-d).

Figure 2 depicts the dissolution data for spheres prepared with 6% w/v glipizide and different carrageenan level. The drug release from spheres prepared with 6% w/v glipizide and 2% w/v Carrageenan was 37.2%, for spheres prepared with 3% w/v Carrageenan was 29.35% and for spheres prepared with 4% w/v Carrageenan was 25.55%. As the level of drug remained constant at 6% w/v and level of polymer increased in the formula, the drug release was decreased.

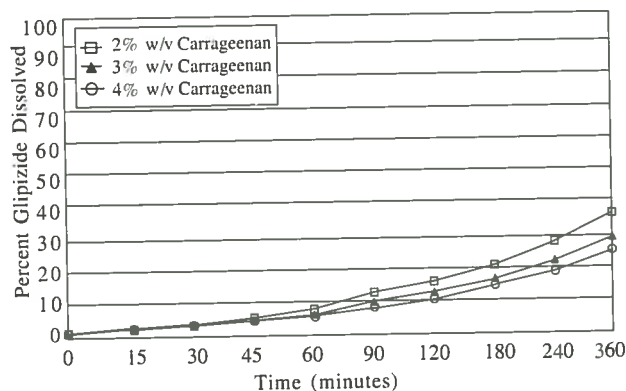


Figure 2. Dissolution profiles for spheres prepared with 6% w/v glipizide and different Carrageenan level.

The same trend was true for spheres prepared with constant level of polymer (3% w/v) and different drug level. At 360 minutes spheres prepared with 3% w/v polymer and 3% w/v drug released 66.9%, spheres prepared with 6% w/v drug released 29.3% and spheres prepared with 9% w/v drug released 26.3% (Figure 3).

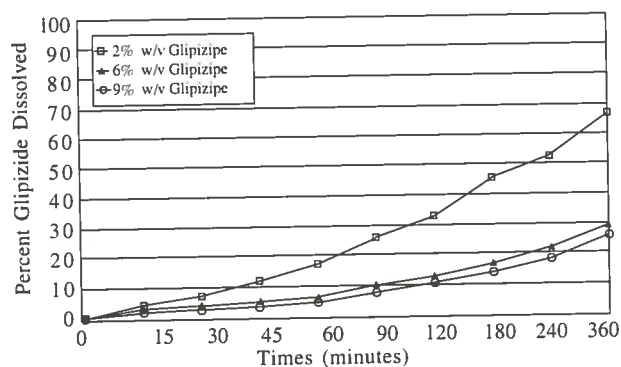


Figure 3. Dissolution profiles for spheres prepared with 3% w/v Carrageenan and different glipizide level.

The diffusion release rate constants for spheres prepared with 6% w/v glipizide and different Carrageenan level 2% w/v, 3% w/v and 4% w/v were 2.39 mg/ \sqrt{t} minute, 1.82 mg/ \sqrt{t} minute and 1.59 mg/ \sqrt{t} minute respectively. As the level of polymer was increased in the formula, the drug

release rate was decreased. The same trend was true for spheres prepared with constant polymer level (3% w/v) and different drug level. The diffusion release rate constant from spheres prepared with 3% w/v Carrageenan and 3% w/v glipizide was 4.39 mg/ \sqrt{t} minute, for spheres prepared with 6% w/v glipizide was 1.82 mg/ \sqrt{t} minute and for spheres prepared with 9% w/v glipizide was 1.66 mg/ \sqrt{t} minute (Table 3).

Table 3. Diffusion Release Rate Constant for Sphere Formulations Prepared by Cross Linking

Test (n=6)	Spheres containing 6% w/v glipizide and different Carrageenan level (% w/v)			Spheres containing 3% w/v Carrageenan and different drug level (% w/v)		
	2	3	4	3	6	9
Diffusion release rate constant (mg /t)	2.39	1.82	1.59	4.39	1.82	1.66
Correlation coefficient	0.994	0.9906	0.9911	0.9971	0.9901	0.9877

All compact formulations from spheres were uniform in weight, and hardness value varied from 8.92-13.57 Kp. Friability percent for all compacts was less than 1% except for tablets compacted from spheres prepared with 6% w/v drug and 2% Carrageenan and tablets compacted from spheres prepared with 3% w/v glipizide and 3% w/v Carrageenan where the percent friability was 1.19% and 3.03% respectively. The disintegration for all formulations prepared was between 15-21 minutes (Table 4).

Table 4. Uniformity of Weight, Hardness, Friability of Tablet Formulations Compacted From Spheres Prepared by Cross Linking Technique

Test (n=10)	Tablets containing 6% w/v glipizide and different Carrageenan level (% w/v)			Tablets containing 3% w/v Carrageenan and different glipizide level (% w/v)		
	2	3	4	3	6	9
Mean weight (mg)	398	402	400	402	402	400
- standard deviation	-5.62	-5.65	-1.93	-5.90	-5.65	-1.52
Mean hardness (Kp)	13.35	13.57	12.52	8.92	13.57	9.05
- standard deviation	-1.98	-2.65	-2.37	-1.65	-2.65	-1.13
Mean friability (%)	1.19	0.68	0.36	3.03	0.68	0.44
- standard deviation	-1.25	-0.25	-0.45	-0.54	-0.25	-0.36
Disintegration time (minutes)	15	17	18	15	17	21

Figure 4 shows the scanning electron photomicrographs for tablets compacted from spheres prepared with 6% w/v glipizide and 2% w/v Carrageenan (Figure 4-a), tablets compacted from spheres prepared with 6% w/v glipizide and 4% w/v Carrageenan (Figure 4-b), tablets compacted

from spheres prepared with 3% w/v Carrageenan and 6% w/v glipizide (Figure 4-c) and tablets compacted from spheres prepared with 3% w/v Carrageenan and 9% w/v glipizide (Figure 4-d). As the level of drug increased in the formula, less cracks and pores appear on the surface of tablets.

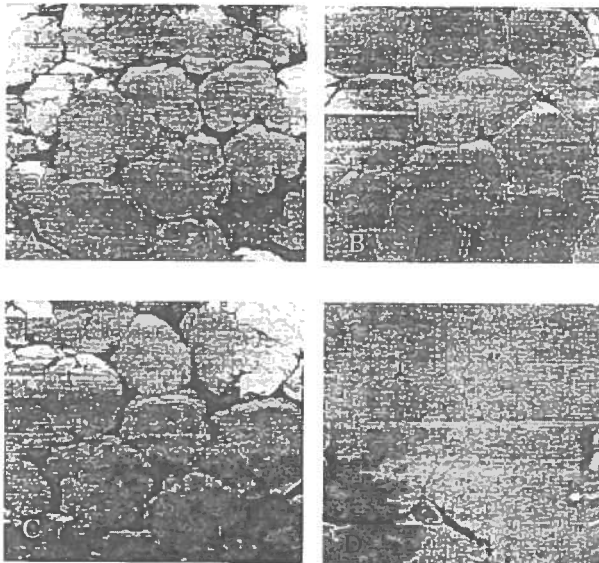


Figure 4. Scanning electron photographs for tablets compacted from spheres prepared with 6% w/v glipizide and 2% w/v Carrageenan (4-a), tablets compacted from spheres prepared with 6% w/v glipizide and 4% w/v Carrageenan (4-b), tablets compacted from spheres prepared with 3% w/v Carrageenan and 6% w/v glipizide (4-c), and tablets compacted from spheres prepared with 3% w/v Carrageenan and 9% w/v glipizide (4-d).

Figure 5 depicts the dissolution profiles for tablets compacted from spheres prepared with 6% w/v glipizide and different Carrageenan level. At 360 minutes of testing dissolution, tablets compacted from spheres prepared with 6% w/v glipizide and 2% Carrageenan released 52% drug,

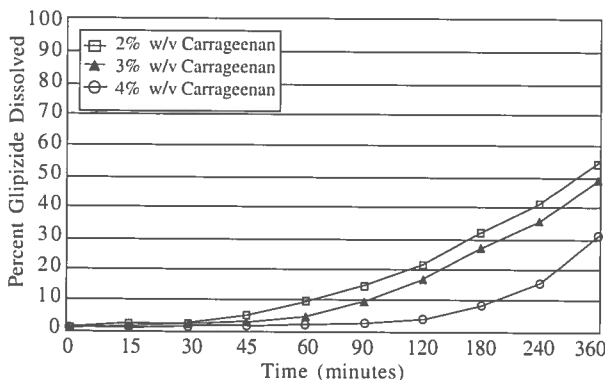


Figure 5. Dissolution profiles for tablets compacted from spheres prepared with 6% w/v glipizide and different carrageenan level.

tablets compacted from spheres prepared with 3% w/v Carrageenan released 46% and tablets compacted from spheres prepared with 4% w/v Carrageenan released only 29% of the drug. The diffusion release rate constants are shown in Table 5. As the percent of polymer was increased in the formula, the drug release was decreased, tablets compacted from spheres prepared with 6% w/v glipizide and 2% w/v Carrageenan was 3.7 mg/ \sqrt{t} minute while the diffusion release rate constant for tablets compacted from spheres of the same composition but prepared with 4% w/v Carrageenan was 1.79 mg/ \sqrt{t} minute.

Table 5. Diffusion Release Rate Constant for Tablets Compacted from Spheres Prepared by Cross Linking Technique

Test (n=6)	Tablets compacted from spheres containing 6% w/v glipizide and different Carrageenan levels (% w/v)			Tablets compacted from spheres containing 3% w/v Carrageenan and different glipizide levels (% w/v)		
	2	3	4	3	6	9
Diffusion release rate constant (mg/ \sqrt{t})	3.7	3.29	1.79	5.2	3.29	2.64
Correlation coefficient	0.990	0.980	0.896	0.995	0.980	0.993

The dissolution profiles for tablets compacted from spheres prepared with 3% w/v Carrageenan and different glipizide levels are shown in Figure 6. Tablets compacted from spheres prepared with 3% w/v Carrageenan and 3% w/v glipizide was 63.2%, for tablets compacted from spheres prepared with 6% glipizide was 34.3% and for tablets compacted from spheres with 9% w/v glipizide was 31%. The diffusion rate constants are shown in Table 5. The diffusion release rate constant was 5.29 mg/ \sqrt{t} minute for tablets compacted from spheres with 3% w/v Carrageenan and 3% w/v glipizide, 3.29 mg/ \sqrt{t} minute for tablets compacted from spheres prepared with 6% w/v

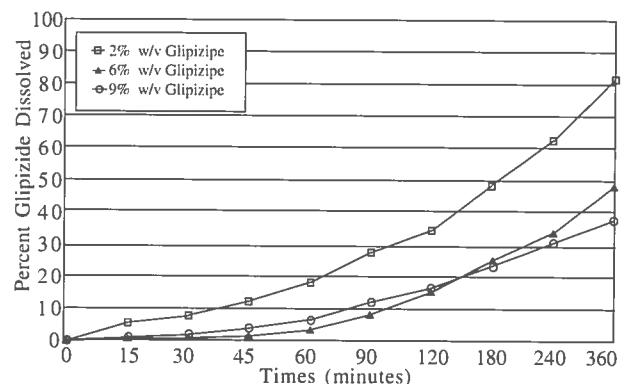


Figure 6. Dissolution profiles for tablets compacted from spheres prepared with 3% w/v carrageenan and different glipizide level.

glipizide and 2.64 mg/ \sqrt{t} minute for tablets compacted from spheres of the same composition but prepared with 9% w/v glipizide.

Conclusions

This investigation demonstrated that spheres and tablets compacted from spheres prepared with the natural polymer, Carrageenan and cross-linking technique can sustain the release of glipizide. Concentrations of 2% or 3% w/v polymer had appropriate viscosity, suitable for suspending different level of the drug. The drug level and the polymer level are determining factors in controlling the drug release from spheres and tablets compacted from spheres. The cross-linking technique is simple, rapid, and can offer the formulator control over drug release.

Resumen

El objetivo de esta investigación fue utilizar el polímero natural Carrageenan para obtener esferas de liberación controlada que contienen glipizide utilizando la técnica de entrecruzamiento. El efecto del nivel del polímero y el contenido de la droga fue investigado. La droga fue dispersada en una solución de Carrageenan y la dispersión fue vertida por un aparato, que contiene 3 agujas desechables, en una solución de entrecruzamiento que contiene 3% de cloruro de calcio. Después de 15 minutos las esferas fueron recogidas por decantación y secadas en un horno con aire caliente a $38^{\circ}\text{C} \pm 2^{\circ}\text{C}$ por 24 horas. Las esferas secas fueron compactadas satisfactoriamente en tabletas utilizando una máquina rotatoria Manesty B-3B equipada con punzones redondos de cava plana con un medida de 12/32 pulgadas; el peso deseado de la tableta fue de 400 mg \pm 5%. Mientras el nivel del polímero fue aumentado en la formulación de la esfera, la liberación de la droga fue aumentado también. Sin embargo, mientras el nivel de la droga fue aumentado en la formulación de esfera, la razón de liberación fue disminuida. Este patrón fue igual para las tabletas compactadas de esferas. El examen con microscopio electrónico mediante fotografías apoya la data de disolución. Hubo más tabletas rotas y con superficies desgarradas en las tabletas compactadas de esferas con un contenido alto del polímero y un nivel bajo de droga.

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