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PREPARATION AND EVALUATION OF *IN VITRO* DISSOLUTION CHARACTERISTICS OF SUSTAINED RELEASE METOPROLOL TARTRATE MICROCAPSULES

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ABSTRACT

Metoprolol tartrate (MT) was encapsulated with Eudragit RS® by an emulsion-solvent evaporation method to develop a controlled release dosage form. This process was efficient, reproducible and not time consuming. Different release characteristics were obtained by changing the drug to polymer ratio and varying the percentage of aluminum tristearate incorporated in the encapsulation medium as a smoothing agent. In the presence of aluminum tristearate, the formed microcapsules were typically spherical and exhibited size distribution within a narrow range. High drug-to-polymer ratio resulted in increased microcapsule size and drug release rate. The microcapsules showed pH-independent dissolution behaviour.

INTRODUCTION

Certainly, controlled release drug preparations -widely used as dosage forms for the treatment of several diseases - have been developed and marketed both in oral and transdermal dosage forms. Advantages and disadvantages of the systemic absorption of drugs by transdermal methods and also controlled delivery using many sub-unit doses in oral dosage forms have been reviewed[1].

Metoprolol tartrate (MT) is a β-adrenergic blocking agent used in the treatment of hypertension, angina pectoris and cardiac arrhythmias. It is rapidly metabolized in man with a plasma elimination half-life of 2-4 h [2]. Because of its relatively short plasma half-life the drug is normally prescribed 2-4 times daily. Treatment for both hypertension and angina is long-term, therefore an effective controlled release dosage form of MT to be taken once or twice a day would be very beneficial to the patient.

Controlled release oral dosage forms can be fabricated as single-unit or multible-unit doses. Microspheres, a multiple-unit dosage form, provide several advantages over other sustained release systems, especially matrix-type tablets. They improve drug absorption and spread smoothly and uniformly in the gastrointestinal tract and cause little risk of side effects [3, 4].

In the present study, MT sustained release microcapsules were prepared with Eudragit RS® by an emulsion –solvent evaporation method. This method is generally known to be simple, reproducible and economical [5,6]. Eudragit RS® is widely used as coating material in the pharmaceutical preparations. Chemically, it is a copolymer synthesized from acrylic and methacrylic esters with a low content of quaternary ammonium groups. Since Eudragit RS® film is only slightly permeable, drug release through the film is relatively retarded.

Thus, the objectives of this study were to prepare microcapsules containing MT, and to investigate the variables affecting the preparation as well as the release properties of the prepared microcapules.

EXPERIMENTAL

Materials:

Metoprolol tartrate U.S.P XXII grade (Helm AG Hamburg Germany), Eudragit RS®100 (Rohm Pharm. Co., Allemange, Germany) and Aluminum tristearate (Nakari Chem. Co., Tokyo, Japan) were used. Acetone (E. Merck, Darmstadt, Germany) and mineral oil (liquid paraffin) were used as dispersion media. N-hexane was used as a washing agent. All other chemicals were of reagent grade and used without further purification.

Preparation of Metoprolol Microcapsules:

Microcapsules were prepared by an emulsion-solvent technique. Eudragit RS was completely dissolved in acetone (30ml). Aluminum tristearate and MT were then added. The mixture was stirred at 250 rpm in 10°C water bath for 20 min and poured into light mineral oil (liquid paraffin, 150 ml) and span 80 (1.5 ml). The system was gradually heated to 35°C in order to evaporate the acetone. After the microcapsules were formed, the liquid paraffin was decanted off and the microcapsules were washed four times with n-hexane (50 ml) and dried under reduced pressure at room temperature. The preparative variables of polymer drug ratio (1:1, 1:3 and 1: 9) and aluminum tristearate concentration were investigated. The distribution of particle size was evaluated by pressing the microcapsules through a set of sieves. To determine the total drug content in the microcapsules; 100 mg of microcapsules were accurately weighed and added into chloroform (30 ml) to dissolve the polymer matrix and MT was then extracted with distilled water (100 ml). The amount of MT in the aqueous phase was assayed spectrophotometrically at 232 nm.

Dissolution Studies:

The dissolution rate of MT from microcapsules was studied in distilled water, 0.1 N HCl (pH 1.2) or sodium phosphate buffer solution (pH 7.4)by using rotating–basket method (100 rpm) at 37± 0.5 °C. Samples of an accurately weighed amounts of microcapsules (equivalent to 100 mg of MT) were taken for the in vitro dissolution studies. The volume of dissolution medium used was 500 ml. Aliquots of the dissolution medium were removed and replaced with fresh medium at appropriate time intervals and assayed for MT by ultraviolet spectrophotometry. All samples were run in triplicate.

RESULTS AND DISCUSSION

Effects of operating conditions and variables on the pelletization of MT:

An emulsion-solvent evaporation method comprises dispersing drug-polymer solution into an immiscible vehicle to form an emulsion. As the solvent is evaporated, the droplets become gradually concentrated and the nucleation takes place. Drug-loaded microcapsules are thus produced[7,8]. Micropelletization using Eudragit RS® was previously investigated in a methylene chloride/water system and the two problems of swelling and fragility have been reported[9]. In this study, the evaporation process in an oil phase (external phase) using liquid paraffin was employed. Since solvents with dielectric constants between 10 and 40 show poor compatibility with liquid paraffin and the systems of these solvents/liquid paraffin were reported to be applicable to the micropelletization process[10], acetone with a dielectric constant of 20.7 was used as a dispersed phase (internal phase).

The rate of agitation, the rate of heating, the polymer/drug ratio and the concentration of additives are important factors which affecting the particle size and shape, the size of distribution and the yield of the microcapsules. Table (1) indicates the MT content of microcapsules and also drug loss. As seen in this table highly drug-loaded microcapsules were obtained. Incorporation efficiency was high since it ranged from 76 % to 87 %. It is clear that drug loading was not affected by drug/polymer ratio. On the other hand, stirring rate during the preparation of microcapsules has shown an influence on the particle sizes of microcapsules. As shown in table 2, increasing the stirring rate decreases the mean diameter of microcapsules and reduces the size of distributions. By an increased stirring rate the resulting finer emulsion produced smaller microcapsules and the increased rate of agitation prevented adhesion of smaller soft microcapsules.

MT microcapsules were also prepared in the presence of different concentrations of aluminum tristearate. Flocculation was clearly recognized when no aluminum tristearate was added into the system. Microcapsules were completely formed in the presence of a small amounts of aluminum tristearate. It was found that with 4% aluminum tristearate, the microcapsules were nearly uniform and free-flowing with a good reproducibility. It has been reported that aluminum tristearate reduces the interfacial tension and prevents electrification and flocculation during the preparation of microcapsules[10]. However, addition of excess aluminum tristearate (7-15%) to the system resulted in a large amount of aggregates since the electric charge of Eudragit RS was reduced progressively by adsorption of aluminum tristearate [11,12]. The actual drug content increased with the amount of aluminum tristearate added. It is considered that aluminum tristearate cooperates to build a dense surface of the microcapsules and prevents leakage of the drug into the dispersion medium during the micropelletization process.

Table (1) Mean particle size and drug content of MT microcapsules prepared in different drug: polymer ratio.

Drug Polymer Ratio	Mean Particle Size	Theoretical Drug Content %	Assay Drug Content %	n Efficiency
1:1	312.8	50.0	39.5	79.0
1:3	247.8	25.0	19.2	76.8
1:9	189.6	10.0	8.7	87.0

Table (2) Effect of stirring rate on the mean particle size of the prepared MT microcapsules.

Stirring Rate	Theoretical Drug Content %	Assay Drug Content %	Particle size
250.0	25.0	19.2	1163.0
450.0	25.0	18.5	296.6
1200.0	25.0	19.0	271.9

Table (3) Entrapment of drug within MT-Eudragit RS microcapsules.

Amount of Aluminum Tristearate (wt %)	MT content (wt %) (Theoretical content 50 %)
1.5	13.27
2.5	26.84
4.0	39.50
7.0	41.46
15.0	43.64

In vitro dissolution studies

The dissolution rate profiles of MT microcapsules determined by the rotating basket method are shown in Figures (1-3) Each point represents the average of three experiments. As shown in Figure (1) the rate of dissolution of MT from Eudragit RS microcapsules was related to the concentration of the polymer used. The higher the polymer/drug ratio, the slower the release rate of the drug. This might be attributed to the lower porosity and thicker wall of the microcapsules that were prepared by using the higher concentration of Eudragit RS. It is considered that a higher polymer/drug ratio results in a longer diffusion path, so that release is retarded. The same observation was also made in another study [13]. Figure (2) shows the release of drug from microcapsules prepared in presence of different concentrations of aluminum tristearate It was found that the most prominent effect on the drug release retardation was attained by using 4% aluminum tristearate.This implies that the microcapsules prepared under these conditions have very smooth and compact surfaces with few pores. The effect of pH of the

dissolution medium on the drug release was investigated. It is clear from figure (3) that the release of drug from Eudragit RS microcapsules is independent of the pH of the dissolution media. Therefore, it is concluded that the drug permeability of Eudragit RS matrix is consistent and drug release is not affected by individual variations within the milieu of the digestive tract.

Drug release mechanism:

The release rates were determined by linear regression analysis using special software program. The main models which have been suggested to describe drug release kinetics from microcapsules are zero-order model, first-order model and matrix model. These models have been discussed and the zero-order model was found to be inapplicable since release was non-linear (Fig.1).

Figure 4 illustrates the release profiles of MT when plotted as the logarithm of the percent remaining drug as a function of time. A linear relationship indicating a first order release was obtained up to the end of 60 min (in case of polymer/drug ratio 1:1) and 3 hr (in the case of polymer/drug ratio 4:1). However, a discontinuous linearity was obtained thereafter, indicating that another mechanism may be followed. It is known that the rate of release from a planar matrix is usually proportional to the square root of time [14], while the release from spherical matrices has been described by Baker and Lonsadle [15]. The release data replotted as a function of square-root of time to test the adaptability of the drug release to Higuchi model. The findings according to Higuchi equation are given in Fig. (5). An equation derived by Higuchi (14) and Baker and Lonsadle [15] was used:

$$3/2[1-(1-F)2/3]-F=K.T$$

Where: F is the fraction of drug released,
K is a constant
and T is the time.

The fraction of the drug released was plotted against time (Fig. 6) to test the adaptability of the release data to the previous equation. It was found that MT release process from its microcapsules obeyed the Baker and Lonsadle model well at a high polymer/drug ratio and deviated slightly at lower polymer/drug ratio. This indicated that the microcapsules exhibited a matrix type drug release.

In conclusion, controlled release microcapsules of metoprolol can be prepared by using the emulsion-solvent evaporation technique. This process is very simple, economical and also convenient to scale up to a commercial level.

The release profiles of these microcapsules can be modified by controlling Eudragit concentration and by changing the aluminum tristearate ratio. In vitro dissolution findings showed that the drug release appeared to fit the Higuchi matrix model.

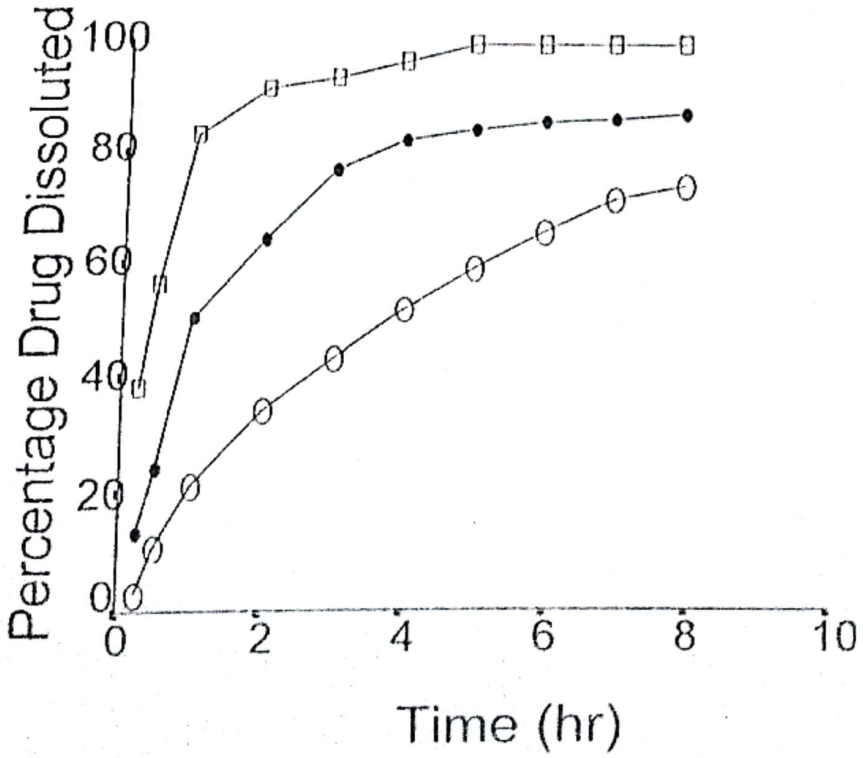

Fig. (1) Effect of different polymer/drug ratios on release profiles of MT Microcapsules. MT:Eudragit RS 1:1 (□), 1:3 (•) and 1:9 (0).

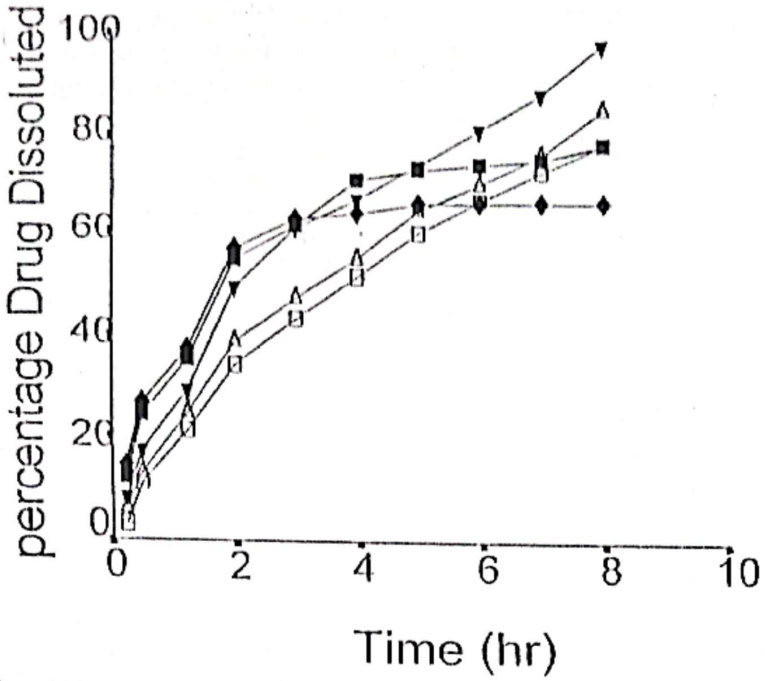

Fig (2) Drug release from MT Eudragit RS microcapsules as a Function of percentage of aluminium tristearate (Δ) 1.5 %; (▼) 2.5 %; (□) 4 %; (♦) 7 %; (■) 15 %.

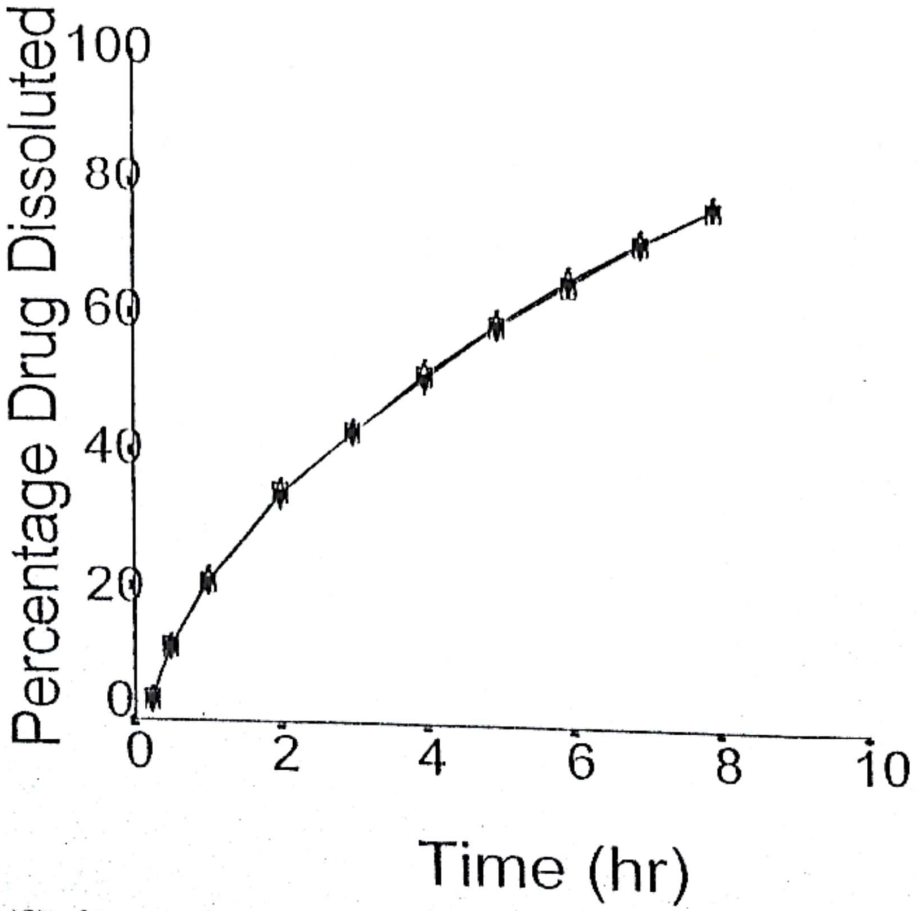

Fig.(3). Drug release from MT-Eudragit RS microcapsules in different dissolution media (Δ) water; (▼) 0.1N HCl; (□) sodium phosphate buffer.

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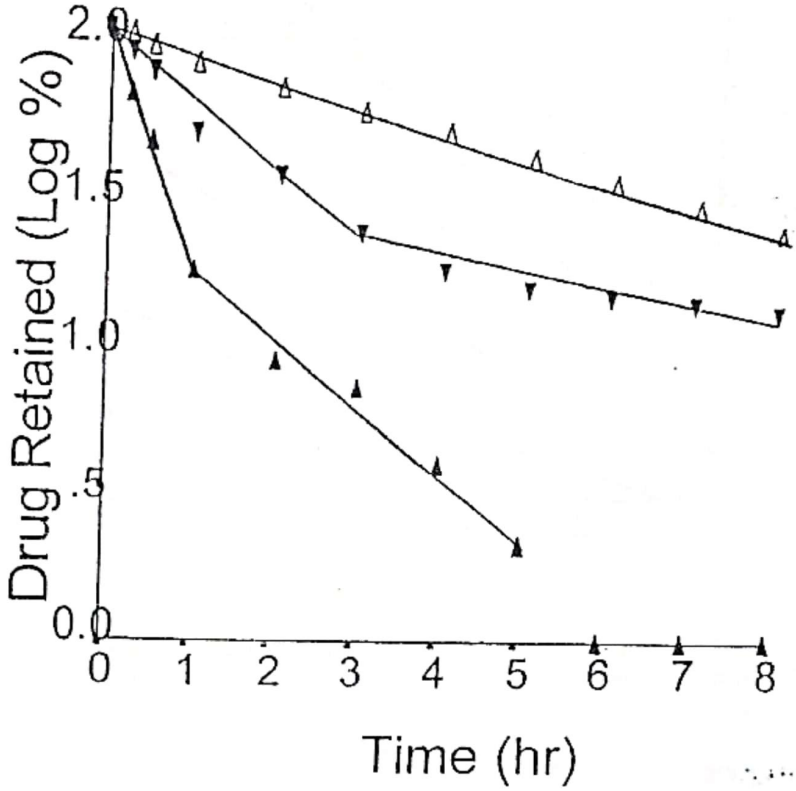

Fig. (4) First-order MT release profiles from microcapsules prepared using different polymer/drug ratios.MT-Eudragit RS 1:1 (▲), 1:3 (▼) and 1:9 (Δ).

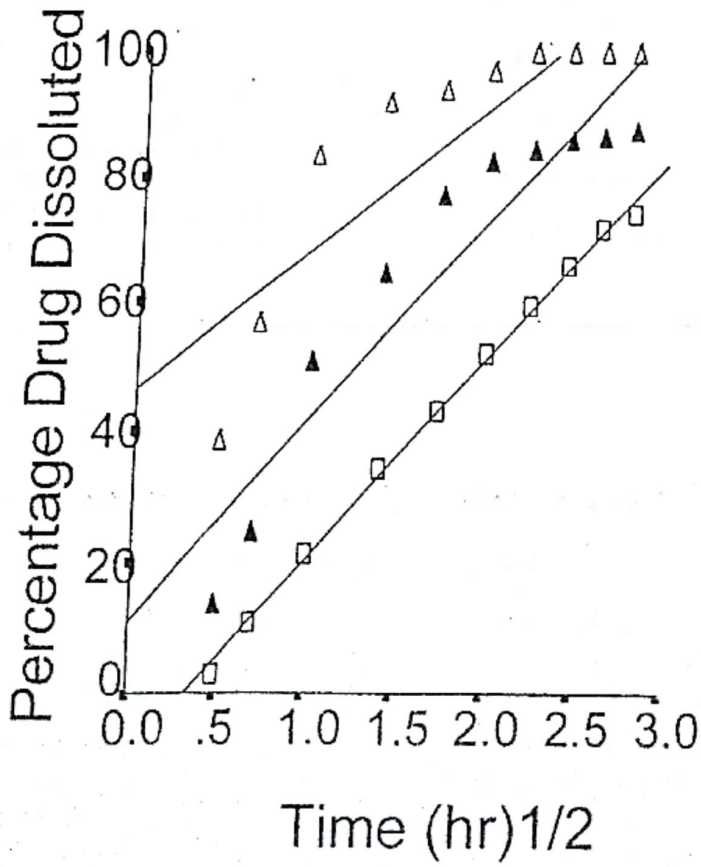

Fig. (5) Release profiles of MT Microcapsules when plotted according to the diffusion model. MT : Eudragit RS 1:1 (Δ), 1:3 (▲) and 1:9 (□)

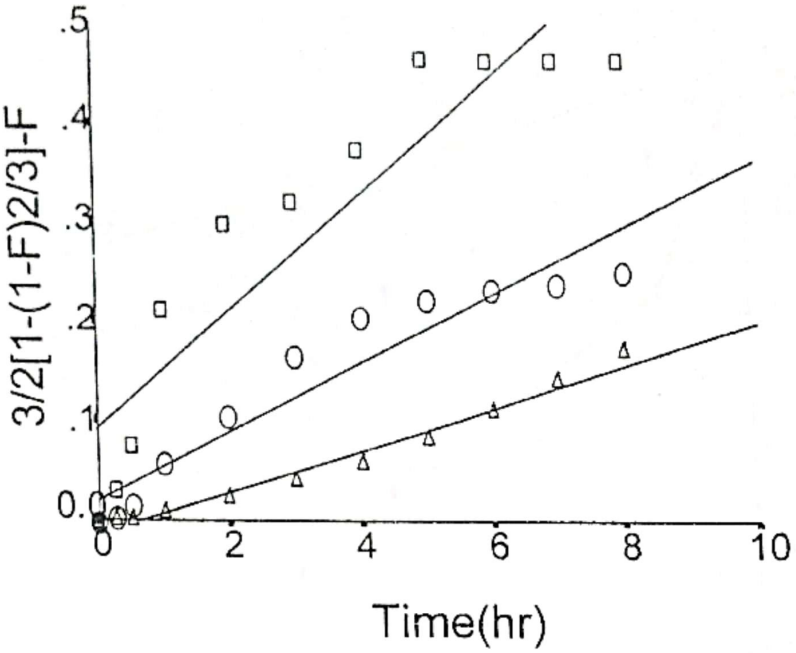

Fig (6) Fraction of drug released from microcapsules plotted against time for batches containing different drug polymer ratios 1:1 (□) 1:3 (0) and 1:9 (Δ).

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تحضير طرطرات ميتوبرولول متحوصلة وممتدة الإنطلاق وتقييم خصائص ذوبانها

محمد مصطفى السيد

قسم الصيدلانيات – كلية الصيدلة – جامعة الزقازيق – مصر

فى هذا البحث تم حوصلة طرطرات الميتوبرولول فى مادة الايدراجيت آر. إس. بواسطة طريقة التبخير للمستحلب مع المذيب بهدف تحضير جرعة منضبطة الانطلاق. وهذه الطريقة سريعة وفعالة وذات انتاجية. وتم دراسة خصائص الانطلاق المختلفة بواسطة تغيير نسبة العقار إلى البوليمر وكذلك النسبة المئوية لثلاثى ستيارات الالومنيوم لمنع التصاق الحويصلات.

وقد ثبت أن الحويصلات التى تتكون فى وجود ثلاثى ستيارات الالومنيوم أتت مستديرة وحجمها متقارب.
كذلك نتج عن استخدام نسبة عالية من العقار إلى البوليمر زيادة فى حجم الحويصلات وكذلك فى سرعة الانطلاق.
وقد أوضحت الدراسة أن خصائص الذوبان للعقار لا تعتمد على الاسى الهيدروجينى للوسط .