Promising Polymeric Buccoadhesive Bilayered Tablets Releasing Valsartan: Effect of Gel Strength

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ABSTRACT

The objective of the present study was to develop buccal bilayered controlled release tablets in order to overcome the poor oral bioavailability of valsartan. They were prepared by direct compression. Various types and amounts of mucoadhesive polymers were investigated. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, and in vitro drug release to optimize the formulation. The tablets containing carbopol 934, hydroxypropyl methyl cellulose (HPMC), sodium alginate in the ratio of 3:2:1, respectively, exhibited a promising mucoadhesive bilayer tablets. They had acceptable physical properties, maximum mucoadhesive strength of 62.68 ± 0.91 g/cm², anomalous (non-Fickian) diffusion with an optimum flux value of 2.2285 μg/cm²/h. The in vitro diffusion studies revealed that the strength of the three dimensional network gel structure formed on the surface of the backing layer played a major role in the drug release. Combining sodium alginate with carbopol-934 created a weak gel structure that enhanced the drug release, whereas the combination of HPMC with carbopol-934 created a strong gel structure that retarded the drug release. FTIR and DSC studies confirmed the postulated intermolecular interaction between the drug and the polymers, which controlled the gel strength and, consequently, the drug release.

Keywords: Valsartan, Mucoadhesive Buccal Tablets, Carbopol.

1. INTRODUCTION

Valsartan is an angiotensin II-receptor blocker. It is widely prescribed in a variety of cardiac conditions such as hypertension, diabetic nephropathy and heart failure. It has low molecular weight (435.5 Da) and melting point of 116-117°C with a log partition coefficient of 1.499, indicating that the compound has a rather hydrophilic character at physiological pH. Valsartan is a white fine powder with two major challenges in its oral delivery. It has the following characteristics: (1) it is slightly soluble in water with strong pH dependent property; and (2) it undergoes first pass metabolism that leads to low bioavailability (approximately 20-25%), and shorter half-life (nearly 6 hours). Moreover, food decreases its peak plasma concentration by about 50%, and its absorption and bioavailability by about 40%

Buccal route provides an excellent easy accessible, better patient compliance route of administration. It avoids the first pass metabolism, which can improve the delivery of valsartan. Definitely, increasing the drug bioavailability may significantly enhance the therapeutic response and reduction in the overall dose. The major challenge for such delivery is the retention of the delivery system in the oral cavity for the desired duration. In addition to the formulation of a unidirectional controlled predictable drug release towards the mucosa, the use of excellent mucoadhesive polymers, such as carbopol, hydroxyl propyl methyl cellulose, sodium alginate, chitosan gives a great opportunity to increase the retention time providing higher absolute bioavailability, and faster absorption rate.
Various bioadhesive mucosal dosage forms have been developed as tablets, gels, disks, patches, and films.

Recently, a variety of drug substances have been investigated as mucoadhesive buccal tablets. Examples include clonazepam, fluconazole, propranolol, ritodrine hydrochloride, and nicotine.

Mucoadhesive tablets can be tailored to satisfy the needs of buccal drug delivery. Ideal mucoadhesive buccal tablets must possess the following properties: (1) good bioadhesive strength so that it can stay in the mouth for a desired duration; (2) non-irritant, do not cause teeth discoloration; (3) provide unidirectional drug release towards the buccal mucosa; (4) resist metabolic barrier; (5) release a drug at appropriate rate; (6) have sufficient tablet hardness; (7) prevent capping and separation of the two individual layers that constitute the bi-layer tablet; (8) prevent cross-contamination between the two layers; (9) produce a clear visual separation between the two layers; and (10) provide accurate and individual weight control of the two layers.

Therefore, the overall objective of the present study was to ascertain the feasibility of in vitro development of bilayered buccal tablets releasing valsartan in a unidirectional controlled manner, and to understand the effect of using different polymers on the mucoadhesive and the release profile of the final formulation.

**MATERIALS**

Valsartan was kindly supplied by Pharma International, Jordan. Carbopol 934 (CP) was kindly supplied by JOSWE, Jordan. Hydroxypropyl methylcellulose (HPMC), mannitol, magnesium stearate, sodium hydrogen phosphate, were purchased from BBC chemicals lab. Sodium alginate was purchased from Sigma, and ethylcellulose (EC) was supplied by Aldrich. All other reagents used were of analytical grade.

**METHODOLOGY**

1. **Preparation of the medicated bilayer tablets**

Bi-layered tablets were prepared by the direct compression technique. The first layer was prepared by properly mixing, for 5 minutes, the accurately weighed drug, talc, magnesium stearate, mannitol and the different ratios of the mucoadhesive polymers as presented in Table 1. The blend was compressed using a hydraulic press with flat-faced punch of 8.5mm diameter followed by a careful removing of the upper punch without disturbing the set up in order to press the accurately weighed 56mg of ethyl cellulose of the backing layer over the mucoadhesive layer.

![Table 1. Buccal tablets composition in mg per each tablet](image-url)
2. In vitro release-dissolution studies

The in vitro drug release studies were conducted using Franz diffusion cells at 37 ± 1 °C. The tablets were placed on a wire mesh, mounted between the two compartments of the diffusion cell, in such a way that the backing layer was facing the donor compartment and the adhesive layer facing the receiver compartment. Samples of 1.0 ml were taken periodically through the sampling port from the receiver cell at predetermined time intervals (0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 and 6.0 hours), and replaced with an equal volume of fresh receptor solution of phosphate buffer (PB) to maintain a constant volume of the receptor phase. Samples were analysed for drug content using UV-spectrophotometer, Schimadzu-Japan. The absorbance of all the resulting solutions was measured at wavelength 250 nm against solvent blank.

3. In vitro diffusion studies

In vitro release experiment did not represent the real situation of the mucoadhesive tablets, where a barrier had to be present in order to simulate the in vivo release. Franz cells with a diffusional area of 2.84 cm² were used to study the drug diffusion at 37 ± 1 °C. A dialysis membrane MWCO 25 KDa previously soaked in the buffer solution for 12 hours was mounted between donor and receiver compartments of the diffusion cell. Tablets were placed on the top of the dialysis membrane, in such a way that the backing layer was facing the donor chamber and the adhesive layer facing the dialysis membrane. Phosphate buffer (PB) of pH 7 was used as a receptor medium and agitated with a magnetic stirrer. Samples of 1.0 ml were taken from the receptor side at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 5.0, 6.0 and 7.0 hours, and replaced with the same volume of phosphate buffer. Samples were analysed for drug content using UV-spectrophotometer, Schimadzu-Japan. Diffusion experiments were conducted in not less than triplicates.

The cumulative amount of the drug diffused (Q) across a unit surface area of mucosal tissue (μg/cm²) was plotted versus time, and the flux (J) was calculated from the slope of the linear (steady state) part of the line obtained using linear regression analysis of the data.

To investigate the unidirectional drug delivery, the back diffusion of the drug across the ethyl cellulose was investigated by taking one sample (1 ml) from the donor compartment, which was previously filled with 2ml of PB. This sample was taken after 24 hours of starting the experiment and was analysed for drug content.

4. Mucoadhesion strength

The mucoadhesion strength was examined (n = 6) using an adopted method described by Dias R.J. et al. with minor modifications. Chicken pouches were used to study the mucoadhesion strength. The freshly cut chicken pouch was excised, washed, equilibrated at 37°C for 30 min in PB and tied tightly over the protrusion in the steel block. On the other side, the tablet was stuck to a cylinder using cyanoacrylate glue and wetted with 1 drop of PB with the mucosal side upwards. The tablet was pasted to the chicken pouch with a constant weight of 50g placed over the tablet for 2 minutes. Mucoadhesive strength was then assessed by adding weights on the down side till the tablet separated from the mucosal surface; in terms of the weight (in g) required to detach the tablet from the membrane.

5. Fourier transform infrared

FTIR spectra of the drug, the polymers and the obtained optimized physical mixture were measured using potassium bromide disc method. The resultant disc was mounted in a suitable holder in Shimadzu FT-IR spectrophotometer and the spectrum was recorded from 4000cm⁻¹ to 400cm⁻¹. The resultant spectra were compared for any spectral changes.

6. Differential scanning calorimeter

DSC curves were obtained using a DSC 821 Mettler-Toledo instrument under a nitrogen gas flow of 60 mL min⁻¹. The sample powders were crimped in hermetic aluminium pan and heated at a rate of 10 °C min⁻¹ from 25 to 300 °C.
7. Physicochemical characterization

The optimized prepared tablets were evaluated for weight variation, hardness, friability, drug content uniformity, swelling index, and surface pH as followed:

**Tablet Thickness:** Twenty tablets were taken randomly. The thickness of each tablet was measured using a micrometer at four different locations, and the mean thickness was calculated.

**Weight Variation:** Twenty tablets were taken at random. Tablets were weighed individually and the average mass was calculated.

**Tablet Hardness (crushing strength):** The Hansaon Research Hardness Tester, USA was used to determine the tablet hardness.

**Tablet Friability:** Ten tablets were weighed and placed in the Erweka Friabilator-Germany, where they were subjected to combined effect of abrasion and shock in the plastic chamber of friabilator revolving at 25rpm for 4 min, and the tablets were then dusted and reweighed.

**Surface pH:** Bottenberg et al. 24 method was adopted to determine the surface pH. The tablets were kept in contact with 2 mL of PB (pH 7 ± 0.05) for 2 hours at room temperature, and the pH was noted by bringing the glass electrode in contact with the swelled tablet surface.

**Drug Content Uniformity:** Ten tablets were dissolved in ethyl alcohol separately and filtered with filter paper (0.45 μm, Whatman, Maidstone, UK). The filtrate was evaporated and the drug residue dissolved in 100 mL of PB (pH 7 ± 0.05). A sample of 5ml was taken, diluted properly and analysed by UV spectrophotometer at wavelength of 250nm.

**Swelling Index:** Ten tablets were weighed separately (W₁) before they were kept in petri dishes containing 2ml of PB (pH 7 ± 0.05). At regular intervals (1, 2, 4, 6 and 8 h), the tablets were removed from the petri dishes and reweighed (W₂) after removing the excess surface water with the filter paper. The swelling index (SI) was calculated using the following formula equation 1:

\[
SI = 100 \left(\frac{W_2 - W_1}{W_1}\right) \quad \text{equation 1}
\]
obtained for all the tablets. The formulation F1 showed the least amount of drug diffusion, while the formulation F6 showed the highest. All the formulations significantly ($p<0.001$) prolonged the diffusion of valsartan across the dialysis membrane as compared with the control solution. The overall diffusion from the control solution of 0.2 mg/ml PB was linear with respect to time ($r^2 = 0.9988$) as shown in Figure 2.

![Figure 1: In vitro diffusion profile of valsartan across the dialysis membrane in PB of pH 7 at 37°C (each bar represents standard deviation of n=3)](image1)

![Figure 2: The in vitro diffusion profile for a control solution of 0.2 mg/ml PB of pH 7 across the dialysis membrane at 37°C (each bar represents standard deviation of n=3)](image2)

The steady state fluxes ($J$) that were calculated from the slope of the linear penetration profile were presented in Table 2. It showed that the highest drug flux was also for the formulation F6 and the lowest for the formulation F1.
Table 2. The steady state fluxes of the in vitro permeability of valsartan through the dialysis membrane in PB of pH=7 at 37 °C (n=3)

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Steady state flux (µg/cm²/h)</th>
<th>Regression coefficient (r²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.3453</td>
<td>0.9815</td>
</tr>
<tr>
<td>F2</td>
<td>1.7616</td>
<td>0.983</td>
</tr>
<tr>
<td>F3</td>
<td>1.289</td>
<td>0.9492</td>
</tr>
<tr>
<td>F4</td>
<td>2.2285</td>
<td>0.9816</td>
</tr>
<tr>
<td>F5</td>
<td>0.5771</td>
<td>0.9271</td>
</tr>
<tr>
<td>F6</td>
<td>3.8541</td>
<td>0.9964</td>
</tr>
<tr>
<td>Control</td>
<td>13.20</td>
<td>0.9964</td>
</tr>
</tbody>
</table>

Obviously, using the mucoadhesive polymers significantly decreased the release rate of the drug. All the polymers used absorbed water and formed a gelatinous barrier layer on the top of the tablet surface. Eventually, the drug release is expected to be dependent on the water diffusion into the matrix system of the tablets, strength of the gel layer produced, and erosion of the polymer. During the study, it was observed that the tablets were initially swelled with no erosion over the period of 24 hours.

Apparently from the overall data, the strength of the gel layer produced played the major role in the drug release. It was found that the presence of CP alone in the formulation F1 retarded the drug release the most. CP was typically used as the primary anionic polymer. It is water-swellable with high molecular weight which forms hydrogel in aqueous solutions. The carboxyl groups provided by the acrylic acid backbone of the polymer are responsible for its properties. Those groups assumed to be protonated at lower pH value which decreased the repulsion between coiled chains, enabling hydrogen bond forming capability with other proton acceptor compound. At the same time, valsartan as shown in Figure 3 is triazole-derived compound with 8 hydrogen bond acceptors. Valsartan most probably interacted with CP through hydrogen bond formation, creating a very viscous rigid structure that retarded the diffusion of the drug the most. Furthermore, at acidic microenvironment pH, valsartan is considered a class II drug according to biopharmaceutical classification system; low aqueous solubility/low permeability. It has two proton dissociating groups, a carboxyl group and a tetrazole. Any interaction with these groups may change the solubility, the dissolution rate and, consequently, the drug release.

In order for the drug to be released, it had to dissolve inside the hydrated polymeric matrices and then released into the medium via diffusion. Since valsartan has low aqueous solubility at low pH with slow dissolution, then definitely its diffusion would be very limited.

![Figure 3: Chemical structure of valsartan](image-url)
permeation to F1, where a synergistic increase in the viscosity was proposed due to higher hydrogen bond formation between the two polymers. This cross-linked interaction probably resulted in rigid structure formation that retarded the drug release.

To provide more acceptable drug release, the three polymers were combined in different ratios as in F4, F5 and F6. The ratios of CP: HPMC: sodium alginate were (3:1:2), (3:2:1) and (1:2:3), respectively. These combinations resulted in a higher amount of drug diffused than F1, where F6 showed the highest amount of drug diffusion, followed by F4 and F5. It was noticed that by increasing the concentration of sodium alginate and decreasing the concentration of CP, the drug release rate from the tablets was found to be significantly increased. Similar results were reported with the release of propranolol hydrochloride using the bioadhesive polymers sodium alginate and CP-934. Higher rate of drug release was attributed to the higher hydration and swelling of sodium alginate than CP.

3. Mucoadhesive strength

Mucoadhesion strength is a crucial property that needs to be preserved in buccal preparations. Therefore, mucoadhesion strength of F4 and F6, which showed the controlled drug release with the highest amount of drug diffusion, were studied. F4 showed a significant higher mucoadhesion strength (178 g; 62.68 ± 0.91 g/cm², n=6) than F6 (72 g; 25.35 ± 0.62 g/cm², n=6). This difference was due to the difference in the amount of CP in the formulation. The effect of increasing CP was more significant than the effect of increasing sodium alginate as previously also supported by Patel et al. 33, where increasing the amount of CP showed an increase in the mucoadhesion time while sodium alginate showed a decrease in a mucoadhesion time. The degree of mucoadhesion depends on the type and the amount of the polymer used, degree of hydration, polymer chain length, and the molecular weight of the polymer. Obviously, CP formed secondary mucoadhesive bonds with mucin as a result of swelling and interpenetration of the polymer chains in the interfacial region, while the other polymers had only weak superficial bioadhesion.

However, increasing the CP concentration and decreasing the sodium alginate and HPMC concentrations from 1:2:3 (F6) to 3:1:2 (F4) CP: HPMC: Sodium alginate respectively, had been found to decrease the surface pH from 5.81 ± 0.11 to 4.00 ± 0.16, which may result in increased buccal irritation.

4. In vitro release study

Overall, F4 was selected as an optimized formulation where the CP content is the highest and the sodium alginate is the least. In vitro release of F4 was studied and compared with an oral marketed valsartan tablets. Figure 4 shows the in vitro release profiles of F4 tablets and the marketed oral one. It shows that the percent cumulative drug released from the marketed oral tablets was much higher than F4. It was very clear that 46% of the marketed drug is released within the first hour in comparison to 4%, which is released from F4. In addition, only 21% of the valsartan was released after 6 hours in contrast to 83.5% from the oral market tablets, which had the same drug content. The release data were analyzed using the well-known semi-empirical power equation:

\[ \frac{M_t}{M_\infty} = k t^n \] equation 2

Where \( \frac{M_t}{M_\infty} \) is the fractional releasing of the drug; \( t \) is the releasing time; \( n \) is the diffusional exponent and \( k \) is a constant, incorporating structural and geometrical characteristics of the buccal device. The value of \( n \) characterizes the type of release mechanism during the dissolution process. A value of \( n = 0.5 \) indicates case I (Fickian) diffusion, \( 0.5 < n < 1 \) indicates anomalous (non-Fickian) diffusion, and \( n = 1 \) indicates case II transport. 33

The estimated value of \( n \) from the linear regression of log (\( M_t/M_\infty \)) versus log \( t \) was between 0.5 and 1.0, indicating that the release of VAL was found to be non-Fickian diffusion. The liquid diffusion rate and the polymer relaxation rate were of the same order of magnitude. The obtained values of \( k \) and \( n \) were 0.6373, 0.828 respectively with \( r^2 \) (correlation coefficient) value of 0.9952.
The unidirectional drug release of valsartan through the backing layer of ethyl cellulose was assured, where the amount of valsartan in the donor compartment after 24h of release was insignificant.

5. Fourier transform infrared

To explicate the interaction between the polymers and valsartan, FTIR was recorded for the drug, polymers and the physical mixture of F4 formulation as shown in Figure 5. Valsartan showed two carbonyl absorption bands (C=O group) at 1738 and 1720 cm\(^{-1}\), imine band (C=N band) at 1617 cm\(^{-1}\) and N-H band at 1592 cm\(^{-1}\). Alterations of those representative peaks of valsartan in the spectrum of the F4 formulation were obvious. The disappearance of the C=N, and N-H peaks of valsartan in the spectra of F4 with the shift of the carbonyl peak to the lower energy suggested intermolecular interactions between the drug and the polymers. These spectra supported the postulation of hydrogen bond formation between the hydrogen bond acceptor valsartan and the proton donor of CP. Similar suggested interaction was postulated by Lee et al.\(^{34}\) for the interaction between the solid dispersion of valsartan, Soluplus® (SP) and D-alpha-tocopherol polyethylene glycol 1000 succinate polymers.

At the same time, carbonyl stretch of the carboxylic group of the CP showed a strong band at 1720 and 1710 cm\(^{-1}\). Hydrogen bond formation or carboxyl group neutralization was most probably the reason behind the slight shift of the carbonyl stretch and the broadness of the peak in F4 spectra. In their study, Islam et al.\(^{35}\) concluded that hydrogenated or neutralized carbonyl peak in the FTIR spectrum of CP showed lower energy peak predominance at 1650cm\(^{-1}\). Furthermore, the disappearance of carbonyl group stretching of sodium alginate at 1616.03 cm\(^{-1}\) in F4 spectra and the absorption band of absorbed water (H-O-H) of HPMC at 1648 cm\(^{-1}\) indicated the polymers interactions.
6. Differential scanning calorimeter

The thermal behaviors of the drug, the polymers, and F4 formulation were evaluated by DSC for further confirmation of the physical interaction. The DSC curve of valsartan had two sharp endothermic peaks at 79 and 100°C. Those temperatures corresponded to water loss and the melting point of the drug. DSC curve of the physical mixture did not show the expected sharp melting peak of valsartan and instead showed overlapped broad endothermic peaks at around 70–100°C, indicating some physical or chemical interaction had disrupted the lattice of valsartan. This confirms the interaction of valsartan with the polymers. Similarly, Skotnicki et al. 36 showed in their DSC studies the incompatibility of Bisoprolol-Valsartan through the disappearance of the sharp melting peak of valsartan.
7. Physicochemical characterization

The physicochemical parameters of F4 were within limit and passed the criteria prescribed by USP. The average weight of the tablets was 269.74 mg. The maximum variation from the average was found to be ±0.26%. Tablet thickness was 4.49 ± 0.03 mm, which assured the uniform drug release profile. Hardness of the tablets was found to be 5.77 kg/cm². In the preliminary studies, the decrease in the hardness was visually obvious upon the addition of sodium alginate proportion in the formulation. The average percentage loss of weight in the friability test was 0.268%. The test was used to evaluate the ability of the tablet to withstand abrasion, capping and chipping in packaging and handling. Drug content was found to be in the range of 93.86 to 96.43%. It indicated uniformity and low intra-batch variability.

In vitro swelling study was investigated to determine the swelling capacity of F4 and the tablet integrity after swelling. Appropriate polymer swelling behaviour is an essential stage for uniform and prolonged release of the drug and effective mucoadhesion. Optimum hydration and the swelling of the mucoadhesive polymers created a proper expanded macromolecular mesh of sufficient size that enhanced the interpenetration of the polymer chains into the mucin. Figure 7 shows the swelling index of the F4, the formulation showed a gradual water uptake with time with circular shape integrity during the studied period. Tablets did not show any appreciable changes in their shape and form during the studied 8 hours of swelling.

![Figure 7: The swelling index of the formulation F4 using PB (pH 7 ± 0.05) (each bar represents standard deviation of n=10)](image)

CONCLUSION

The study ascertained the feasibility of developing bilayered mucoadhesive tablets with optimal mucoadhesion and ensured unidirectional controlled drug release profile for valsartan. The study of drug release kinetics indicated anomalous (non-Fickian) diffusion. The combined use of Carbopol 934: HPMC: sodium alginate in a ratio of 3:1:2 demonstrated optimized formulation (F4) with maximum mucoadhesive strength, 62.68 ± 0.91 g/cm² and an optimum flux value of 2.2285 μg/cm²/h, while the use of EC ensured unidirectional drug release profile. Using sodium alginate in the formulation helped to weaken the three dimensional gel structure that formed on the top of the backing layer which consequently permitted more drug release than the formulation containing carbopol.
only. A postulated interaction between the valsartan and the carbopol was evident by the FTIR and DSC studies and provided a promising controlled buccal delivery releasing valsartan over prolonged period of time. However future long term stability studies and in vivo clinical studies need to be conducted for the F4 formulation using a suitable animal/human model to continue the potential of the developed transmucosal delivery system.

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Promising Polymeric Buccoadhesive...


النقطة الأولى: 

ностью أقراص مبلمرة فموية لاصقة ثنائية الطبقات تحتوي على الفالساتران: تأثير الهيكل الهلامي على تحرير الدواء

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ملخص

يتهدف هذا البحث إلى تطوير أقراص فموية لاصقة ثنائية الطبقات من أجل التغلب على ضعف التوازي الحيوي الفموي لدواء الفالساتران. تم إعدادها عن طريق الضغط المباشر حيث تم دراسة خلط أنواع وكميات مختلفة من البوليمرات ومن ثم تقييم تفاوت الوزن للأقراص، السمنة، الصلابة، القابلية للتخفيف، درجة التلاصق للغشاء المخاطي، معدل الانفاخ، وعملية تحميل وإفراغ الدواء خلال الفضاء الخارجي. أظهرت الأقراص التي تحتوي على مادة كاربوبول 934، أسيتوكسي بروبيل ميثيل السيكلوز، أليفات الصوديوم بنسبة 3: 2: 1، على التأريخ نتائج واعدة. حيث كان لديهم خصائص فيزيائية مفيدة، وقوة التصاق مخاطية عالية تقدر بـ 62.68 ± 0.91 غرام / سم². وقطرة على تحرير الدواء تمثل ثابت على مدى فترة طويلة من الزمن بالمقارنة مع أقراص الفالساتران الفموية سريعة التحريك. وكتففت دراسات الفحص أن الهيكل الهلامي مكوني الأبعاد المتوازي على سطح الإغلاق دفع نبضًا رئيسًا في تحرير الدواء، حيث أن خط الأليفات الصوديوم مع كاربوبول-934 هيكلاً هلامياً ضعيفًا عزر تحرير الدواء، بينما خلط الكاربوبول-934 مع أسيتوكسي بروبيل ميثيل السيكلوز خلق هيكلاً هلامياً قويًا أعلى تحرير الدواء، واستخدام FTIR وDSC تم تأكيد التفاعل بين الدواء والبوليمرات التي سيطرت على قوة الهيكل هلامي وتحرير الدواء.

الكلمات المفتاحية: أقراص فموية ثنائية الطبقات، فالساتران، كاربوبول.