Formulation of Pulsatile Delivery of Ramipril: A Chrono-Pharmaceutical Approach for the Treatment of Hypertension

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ABSTRACT
The aim of present study was to formulate and evaluate oral multiparticulate pulsatile release of ramipril based on chronopharmaceutical approach for the treatment of hypertension. In the present study the immediate release core mini tablets were prepared by direct compression by using various proportions of different superdisintegrants. The optimized core tablets were then coated with pH sensitive polymers like Eudragit -S100 and Eudragit- L100. To achieve the desired dissolution profile, various parameters like coating duration and coat thickness studied. The coated tablets were evaluated for hardness, thickness, friability, weight variation, drug content, and disintegration time and in-vitro drug release. In-vitro drug release was found to be 98 % from coated tablets in 20 min after 5 hrs lag time. FT-IR spectra revealed that there is no chemical incompatibility between the drug and other excipients. Scanning electron micrograph of optimized tablet shown that the thickness level in the coating. The results concluded the programmable pulsatile release has been achieved from coated tablets after a lag time of 5 hrs, which is consistent with the demands of the chronotherapeutic drug delivery and increasing bioavailability.

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Introduction

Ramipril is an Angiotensin-converting Enzyme Inhibitor, Antihypertensive agent. It is chemically \((2S,3aS,6aS)-1-[(2S)-2-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl] amino] propanoyl] 3, 3a, 4, 5, 6, 6a-hexahydro-2H cyclopenta [d] pyrrole-2-carboxylic acid. Ramiprilat is the active metabolite of Ramipril, competes with angiotensin I for binding at the angiotensin-converting enzyme, blocking the conversion of angiotensin I to angiotensin II. As angiotensin II is a vasoconstrictor and a negative-feedback mediator for rennin activity, lower concentrations result in a decrease in blood pressure and an increase in plasma rennin\(^1\,^2\).

Pulsatile drug delivery aims to release drugs on a programmed pattern i.e. at appropriate time and/or at appropriate site of action. Currently, it is gaining increasing attention as it offers a more sophisticated approach to the traditional sustained drug delivery i.e. a constant amount of drug released per unit time or constant blood levels.

Pulsatile drug delivery systems (PDDS) are characterized by at least two distinctive drug release phases following a predetermined lag time. Drug’s release may be controlled by time, by site or a combination of the two parameters. A delayed release delivery system (where time controls the release) would meet the needs of chronopathologies with symptoms mostly recurring at night time or in the early morning whereas site-specific delivery in to the colon might enable an improvement in the treatment of inflammatory bowel disease and, hopefully in the oral bioavailability of peptide drugs. In time controlled delivery systems, the release profile is determined by formulation parameters while in site specific controlled delivery systems the release profile is determined by parameters related to gastrointestinal environment. Time controlled systems are divided into those using barrier technologies around the active agent designed to degrade or dissolve after a certain time, and in those that the degradation of the polymer itself induces the release of the active agent.

Delivery systems with a pulsatile release pattern are receiving increasing interest for the development of dosage forms, because conventional systems with a continuous release are not ideal. Most conventional oral controlled release drug delivery systems release the drug with constant or variable release rates. A pulsatile release profile is characterized by a time period of no release rates (lag time) followed by a rapid and complete release\(^3\,^4\).

The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation. Pellets and mini tablets considered as multi particulate systems\(^7\,^9\).

Mini-tabs are small tablets with a diameter typically equal to or less than 4mm that are typically filled into a capsule, or occasionally, further compressed into larger tablets. It is possible to incorporate many different mini-tablets, each one formulated individually and programmed to release drug at different sites within the gastrointestinal track, into one capsule. These combinations may include immediate release, delayed release, and/or controlled release mini-tabs. It is also possible to incorporate mini-tabs of different drugs to treat concurrent diseases or combinations of drugs to improve overall therapeutic outcome, while delivering distinct release rates of each according to disease requirements. Mini-tabs could also offer a solution to the current issue in the pharmaceutical industry representing a lack of dosage forms which are suitable for
pediatrics. Mini tablets technology combines the advantages of multi particulate dosage forms with established manufacturing techniques used in tableting. Additional benefits of mini tablets include excellent size uniformity, regular shape and a smooth surface thereby offering excellent substrate for coating with modified release polymeric systems. The drug release profile in multiparticulates can be modified by coating them. Reasons for the application of coating onto multiparticulates are to obtain functional coats, provide chemical stability, improve physical characteristics and enhance patient acceptance\(^\text{10,11}\).

**Materials and Methods**

**Materials**

Ramipril was chosen as a model drug and obtained from Dr. Reddy’s laboratory as a gift sample. Sodium starch glycinate, croscarmellose sodium and crospovidone used as superdisintegrants, microcrystalline cellulose used as diluent and obtained from Vijlak Pharma Limited, PVP K-30 used as binder and obtained from Hetero Drugs, Eudragit L 100, S 100 used as pH sensitive polymers and obtained from Dr. Reddy’s laboratory.

Acetone, Iso propyl alcohol (TKM Pharma) used as solvent mixture for coating, triethyl citrate (TKM Pharma) used as a plasticizer and titanium dioxide used as opacifier and talc used as anti-tacking agent.

**Methodology**

**Preparation of core mini tablets**

Mini tablets of Ramipril were formulated by incorporating superdisintegrants like sodium starch glycinate, croscarmellose sodium and crospovidone, poly vinyl pyrrolidone-k 30 (binder), MCC (diluent), magnesium stearate and talc etc. The core tablets containing Ramipril (1.25mg each tablet), superdisintegrant, poly vinyl pyrrolidone-k 30 and microcrystalline cellulose (Avicel® PH102) were prepared by direct compression. Initially, the core tablet excipients were dry blended for 10 min, followed by the addition of magnesium stearate and talc. The powder components were further blended for 5 min. Direct compression of mini tablets was done in rotary compression tablet machine (Rimek mini press I) using 4mm concave punch. Table 1 describe composition of the uncoated mini-tablets

**Optimization of core mini tablets**

The core mini tablets were optimized based on the disintegration time and dissolution (in-vitro drug release studies) by using the different superdisintegrants and their concentration.

**Coating of mini tablets**

**Preparation of coating solution**

Add the EUDRAGIT® powder slowly into 50% of the diluent mixture and stir until the polymer is completely dissolved (approx. 30–60 minutes). Add talc, titanium dioxide and triethyl citrate in the remaining diluent mixture and stir for 10 minutes with a high shear mixer. Pour the excipient suspension slowly into the EUDRAGIT solution while stirring with a conventional stirrer. Pass the spray suspension through a 0.5mm sieve\(^\text{12}\).

**Coating optimization parameters**

**Equipment setup**

- Drum speed : 8–10rpm
- No. of spray guns : 1
- Nozzle bore : 1.2mm
- Distance tablet bed/spray gun : 10cm
- Internal silicone tube diameter: 2mm

**Process data**

- Inlet air temperature : 40–50°C
- Exhaust air temperature: 25–30°C
Product temperature : 25–30°C
- Difference pressure : 98pa
- Spray rate : 3–6 g/min/kg

The optimized core tablets were subjected to coating with different coating solutions as per coating composition described in table 2. The mini tablets were coated with aqueous ethanolic solution of Eudragit-L 100 and Eudragit-S 100 using a pan coating system by using above coating parameters. Percentage weight gain calculated by the following equation:

\[
\text{Percentage weight gain} = \frac{W_f - W_o}{W_o} \times 100
\]

Where, \( W_i \) = Weight of tablet after coating

Characterization of core and coated tablets

Pre-compression Blend Characterization

The pre-compression blend of mixture containing different concentrations of superdisintegrants was evaluated for angle of repose, Bulk Density, Tapped Density, Carr’s Index and Hausner’s Ratio.

General parameters

Both core and coated tablets were evaluated for hardness (Monsanto hardness tester), friability (Roche friabilator), thickness (vernier calipers) and weight variation.

Content uniformity

Four mini-tablets were weighed and crushed in the mortar. The powder equivalent to 1.25mg of the drug were weighed and dissolved in 100ml phosphate buffer pH 6.8 to give a concentration of 12.5µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 214nm using UV Visible spectrophotometer (Lab India, UV-3200).

Disintegration time

The in-vitro disintegration time for immediate release core tablets were determined by using Disintegration test apparatus (Lab India, DT-1000) as per IP specifications. Place one tablet in each of the six tubes of the basket. Add a disc to each tube and run the apparatus using 900ml of phosphate buffer pH 6.8 as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in phosphate buffer pH 6.8 maintained at 37°C. The time in seconds with complete disintegration of mini-tablets without any palpable mass remaining in the apparatus was measured and recorded.

Dissolution studies for core tablets

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800).

The dissolution fluid was 900ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37°C were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2 min and assayed for Ramipril by measuring absorbance at 214nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8.

Details

<table>
<thead>
<tr>
<th>Apparatus used</th>
<th>USP II Lab India DS 800</th>
</tr>
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<tr>
<td>Dissolution Medium</td>
<td>Phosphate buffer PH 6.8</td>
</tr>
<tr>
<td>Dissolution Medium volume</td>
<td>900ml</td>
</tr>
<tr>
<td>Temperature</td>
<td>37°C</td>
</tr>
<tr>
<td>Speed of paddle</td>
<td>50rpm</td>
</tr>
<tr>
<td>Sampling Interval</td>
<td>2, 4, 6, 8, 10, 12, 14, 16, 18 &amp; 20 min</td>
</tr>
<tr>
<td>Sample withdrawn</td>
<td>5ml</td>
</tr>
<tr>
<td>Absorbance measured</td>
<td>214nm</td>
</tr>
<tr>
<td>Beers Range</td>
<td>2-100µg/ml</td>
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</tbody>
</table>

Dissolution studies for coated tablets

Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50rpm and 37±0.5°C has usually been conducted in different buffers for
different periods of time simulated GIT pH and transit time that the pulsatile delivery system might encounter in-vivo. The samples were withdrawn at regular time intervals and the same volume of dissolution medium was replaced, the samples were analyzed for the release of drug by UV spectrophotometer (Lab India, UV-3200).

Two different dissolution media were used during dissolution.

Surface morphology and film thickness of coated tablets

The optimized coated and uncoated tablets were tested for scanning electron microscopy (STEREO SCAN S 120, Cambridge UK) to know the thickness of the coating layer of the coated tablets when compared with uncoated tablets.

Stability studies

Optimized formulation was subjected to stability studies as per ICH guidelines at 30°C/65% RH and 40°C/75% RH for 2 months. Sample were taken and analyzed at time interval. Selected formulation were subjected to stability studies as per ICH guidelines sample were taken and analyzed at time interval of 15 days for 2 months\(^{16-17}\).

Results

Melting point

Melting point of Ramipril was determined by capillary method. Melting point was found to be in the range of 108-109°C which compiles the standards thus indicating that purity of the drug sample.

Pre-compression Blend Characterization

The pre compression blend of mixture containing different concentrations of superdisintegrants was evaluated for angle of repose, Bulk Density, Tapped Density, Carr’s Index and Hausner’s Ration. There was no much difference in the pre compression Blend Densities as shown in Table-3 for different superdisintegrants.

Drug –excipient compatibility studies by FT-IR

Drug- excipient interactions play a crucial role with respect to the stability and potency of the drug. FT-IR techniques have been used to study the physical and chemical interaction between drug and excipients used.

There was no significance difference between the absorption peaks of pure drug and optimized formulation. The results concluded that there was no interaction between pure drug and excipients.

All the tablets were in concave oval shape and all the uncoated tablets were white in color. Thickness of the all uncoated formulations was found to be 1.62±0.147 to 1.75±0.162mm with low standard deviation values. The crushing strength of the uncoated tablets of each batch ranged between 3.41 to 3.96kg/cm\(^2\). This ensures good handling characteristics of all batches. The % weight variation was calculated for all formulations. All the formulations (f1-f9) were passed the weight variation test as the % weight variation was within the pharmacopoeia limits. The weights of the all formulations found to be uniform with low standard deviation values. The values of friability test were in the range from 0.61 to 0.79%. The per cent friability of all the formulation was less than 1% ensuring that the tablets were mechanically stable.

The values of disintegration time reported in the table. The disintegration time found in the range of 3.75 min to 5 min ensuring that all the core tablets were rapid disintegrating type. The percentage of drug content for all formulations found to be in the range of 92.78-97.85%. It complies with official specifications.

The in-vitro drug release study for uncoated tablets was carried out in pH 6.8 as dissolution medium for about 20 min. The drug release from the formulations increased
as the concentration of super disintegrant increased. Based on the results obtained F3 formulation which was formulated by using 4% Sodium starch glycollate was found to be 97.76% within 14 min and selected for further coating process.

The optimized F3 uncoated tablets were coated by different coating solutions. Coated tablets were red in color, the thickness of the coated formulations ranged between 1.85±0.102 to 2.11±0.132mm. The hardness of the coated tablets ranged from 4.28 to 4.87kg/cm² and the coated tablets weight was increased up to 15 & 30%.

Coating was done with pH sensitive polymers like Eudragit S100 and L100 (F10-F13). The dissolution was carried out by using 0.1N HCL (1.2 pH) & 6.8 pH phosphate buffer.

In-vitro drug release studies were carried out for 5hrs and found to be good sustaining efficacy. The enteric coat of all the four formulations was intact for 2hrs in 1.2 pH but very slowly dissolved in intestinal pH. Based on the thickness of the coating layer of F10 and F11 the drug was released after 4hrs only and F12 and F13 the drug was released after 5hrs.

For F10 and F11 the drug was released within 262 min because of the less % weight increase and for F12 and F13 the drug was released within 320 min.

F12 releases the drug 96.6% within 16min after a lag time of 5hrs. In all the four formulations (F10-F13) the F12 formulation which was coated with Eudragit S100 (9.35%) having better drug release after a lag time of 5hrs and followed by rapid release with in 16 min.

On considering some important parameters like disintegration time, percentage drug content, hardness and in-vitro drug release study, F12 was selected as the best formulation.

The surface morphology and thickness of the F12 formulation and the core tablets were studied under SEM (Stereo scan S 20, Cambridge, UK) and the results concluded that the coating was uniform throughout the core tablet with increased thickness for the coated tablet and the average thickness of coated tablet was found to be 33.28μm.

The results of stability studies were conducted as per ICH guidelines. After 2 months the physical parameters of the tablets like shape, color was same and Tablets were passing the stability studies. The tablets were tested for drug content at 15 days, 1 month and 2 months.

Discussion

Advances in chronobiology and chrono pharmacology has demonstrated the importance of biological rhythms in treatment of disease and this has led to a new approach to the development of novel drug delivery system-ChrDDS (Chronotherapeutical Drug Delivery System). As timing of drug administration in disease therapy has significant impact upon treatment success, ChrDDS in future is certainly going to gain popularity. Chronopharmaceutics will certainly improve patient outcome and optimize disease management in the future. Research in chronopharmacology has demonstrated the importance of biological rhythms in drug therapy and this has led to a new approach to the development of drug delivery systems. Different technologies have been applied to develop time-controlled, pulsed, triggered and programmed drug delivery devices in recent years. Since it is seems that timing of drug administration in disease therapy has significant impact upon treatment success, chronotherapeutics remains an important area for continuing research.

Pulsatile drug delivery aims to release drugs on a programmed pattern i.e. at appropriate time and/or at appropriate site of action. Currently, it is gaining increasing
attention as it offers a more sophisticated approach to the traditional sustained drug delivery i.e. a constant amount of drug released per unit time or constant blood levels.

A delayed release delivery system (where time controls the release) would meet the needs of chronopathologies with symptoms mostly recurring at night time or in the early morning whereas site-specific delivery in to the colon might enable an improvement in the treatment of inflammatory bowel disease and, hopefully in the oral bioavailability of peptide drugs.

The Chrono-study was an attempt made by the authors of the present paper to understand the real world conditions of to test the efficacy of a controlled onset, extended release formulation of ramipril for lowering morning blood pressure. Because risk of myocardial infarction and stroke increases during the rise of blood pressure that many patients experience a rise in the morning, the dose was timed to provide the greatest possible anti-hypertensive effect during this period. F12 formulation from the present study with lag period of 5hrs may definitely produce the effect by reducing systolic blood pressure and diastolic blood pressure under these conditions.17

The chronotherapeutic delivery of ramipril significantly may reduce the circadian BP, heart rate, and the rate-pressure product. With the help of this pulsatile delivery approach of ramipril and drug releasing after 5 hrs will definately achive the hypotheiss of reduction of morning blood pressure which inturn may reduce risk of stroke and myocardial infarction.18

Ramipril delayed release tablet was developed by coating with pH sensitive polymers like Eudragit S100 and L100 (F10-F13). The dissolution was carried out by using 0.1 N HCL (1.2 pH) & 6.8 pH phosphate buffer. Further, in-vitro drug release studies were carried out for 5 hrs and found to be good sustaining efficacy. The enteric coat of all the four formulations was intact for 2 hrs in 1.2pH but very slowly dissolved in intestinal pH. Based on the thickness of the coating layer of F10 and F11 the drug was released after 4 hrs only and F12 and F13 the drug was released after 5hrs.

Thus, we may need to explore the above formulation in human clinical trials for a better proof of reduction possibility of hypertension, in turn to reduce the risk of stroke and myocardial infarction.

**Conclusion**

In the present study, a multiparticulate formulation pulsatile release system for anti-hypertensive drugs with appropriate amounts of excipients is developed. The effect of type and amount of superdisintegrants and type and concentration of polymer on % drug release of pulsatile formulation is studied further. FTIR studies concluded that there was no interaction between drug and excipients. Based on disintegration time and dissolution time the formulation (F3) which contains 4% sodium starch glycollate was optimized. The optimized formulation F3 was further coated with different concentrations of pH sensitive polymers like Eudragit-S100 and Eudragit-L100. Based on the thickness of the coating layer and solubility of the coating layer and the dissolution data, the formulation (F12) was developed with a coating of 9.75% Eudragit-S100 and thus optimized. The optimized formulation successfully resulted in the lag time of 5 hrs and followed by rapid release of drug. The optimized coated and uncoated tablets were further tested for scanning electron microscopy to know the thickness of the coating layer of the coated tablets when compared with uncoated tablets. The stability studies were performed for optimized formulation.
Acknowledgement

We thank Prof. Dr. P. Rajeshwar Reddy (Chairman-Anurag Group of Institutions, Ghatkesar, India) for helpful discussion and motivation. Also, we thank Dr. Prakash V Diwan (Director-School of PHarmacy, Anurag group of Institutions, Ghatkesar, India) for continuous moral support to complete this work with great ease.

Authors’ Statements (Competing Interests)

The authors declare no conflict of interest.

References

### Table 1. Composition of various mini tablet formulations

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<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
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<td>Ramipril (mg)</td>
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<td>1.25</td>
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<tr>
<td>SSG (mg)</td>
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<td>0.9</td>
<td>1.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>CCS (mg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.6</td>
<td>0.9</td>
<td>1.2</td>
<td>-</td>
<td>-</td>
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<td>CP (mg)</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.6</td>
<td>0.9</td>
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<tr>
<td>PVP-k30 (mg)</td>
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### Table 2. Composition of various mini tablet formulations

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<td>Eudragit-S100(g)</td>
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<tr>
<td>Eudragit-L 100(g)</td>
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<tr>
<td>Tri ethyl citrate(g)</td>
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<td>Titanium di oxide(g)</td>
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<td>Acetone(g)</td>
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<td>Water(g)</td>
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Table 3. Flow properties of different formulation blend

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<th>Formulation</th>
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<th>Bulk density</th>
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<td>F2</td>
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<td>25.28</td>
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<td>F4</td>
<td>25.11</td>
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<tr>
<td>F5</td>
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<td>0.81</td>
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<td>F6</td>
<td>26.76</td>
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<td>F7</td>
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<td>0.67</td>
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<td>F9</td>
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Figure 1. Determination of lambda max and construction of Calibration curve
Figure 2. FT-IR spectrum of Ramipril pure drug, excipients and optimized formulation

Figure 3. Cumulative percentage drug release of core tablets with superdisintegrant SSG, CCS (*All the values are mean of three determinations)
Figure 4. Cumulative percentage drug release of core tablets with superdisintegrant CP (*All the values are mean of three determinations)

Figure 5. Cumulative percentage drug release of coated mini tablets with 0.1N HCl and phosphate buffer 6.8 pH
**Figure 6.** Surface morphology of uncoated (A), coated (B) tablets.

**Figure 7.** Transverse section (avg. thickness) of Coated Minitablet.