RESEARCH ARTICLE

Design and Development of Novel Mini Tablet Cap Technology for the Treatment of Cardiovascular Diseases

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ABSTRACT

Objectives: The purpose of the investigation was to extend and evaluate the novel mini tablet cap for treating cardiovascular disease at a desired combinational therapeutic activity and to improve patient compliance. A cheap four-in-one pill can guard against heart attacks and stroke.

Methods and Materials: The drug product was manufactured by mini tablet cap technology. The technology was designed to initially use hydrochlorothiazide, simvastatin immediate release, metoprolol succinate, and asprin sustained release to reach the therapeutic levels at prolonged therapy. The two mini-bilayer tablets were prepared by wet granulation method and compression coated with a hydrophobic and hydrophilic polymer like ethyl cellulose and super disintegrating agents to release simvastatin and hydrochlorothiazide immediately.

Results: Fourier transformer infrared spectroscopy (FTIR) studied the interaction studies of four chosen drugs. The mini tablet cap technology was designed as two mini bi-layer tablets in a capsule. The quantitative detection of four individual drugs was determined by using the RP-HPLC method. It was found that RP-HPLC is sensitive, reproducible, and valid for determining the mini tablet cap. The *in-vitro* drug release studies found that simvastatin and hydrochlorothiazide release 90% immediately within 20 minutes. Metoprolol and aspirin controlled the release for up to 24 hours, and drug release kinetics found that the drug release behavior of the optimized formulation followed first-order kinetics.

Conclusion: The mini tablet cap is one of the best dosage forms to treat cardiovascular diseases. Because it was reported, the combination of these four drugs reduces mortality by 83% in high-risk patients with heart diseases, hypertension, diabetes, and obesity. The novel mini tablet cap approach data revealed a promising formula for improved relief of patient complaints during treatment or prevention of cardiovascular diseases.

Keywords: Mini tablet cap technology, Cardiovascular diseases, Metoprolol succinate, Hydrochlorothiazide, Aspirin, Simvastatin, TIPS.

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INTRODUCTION

Drug formulations containing more than one active ingredient are used to increase patient compliance. Treatment of various diseases often requires oral administration of various drugs to achieve effective results. Different methods of different drugs can lead to many negative and negative effects on the treatment. These can result from the misadministration of multiple supplements, drug-excipient interactions, drug-drug interactions, and poor patient compliance. For example, people with heart disease are often treated with other medications. Most heart conditions require regular monitoring.[1] High blood pressure is one of the most significant modifiable threat factors for heart disease. Beta-blockers can cause sodium and water retention. Metoprolol succinate is a beta-adrenergic blocker

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widely used to manage hypertension and many other heart diseases. Diuretics may also be used with other medications to treat high blood pressure. It inhibits sodium reabsorption from the distal convoluted tubule, resulting in a strong excretion of Na and water as well as Ka and hydrogen ions. Diuretics can cause volume depletion, which increases renal secretion of renin. Another combination drug, simvastatin, is a cholesterol-lowering drug that blocks the production of cholesterol in the body. It lowers low-density lipoprotein (LDL) and cholesterol and helps prevent heart disease and atherosclerosis, thereby preventing heart disease, stroke, and vascular disease.[2]

Control the amount of cholesterol in the body. The use of simvastatin leads to reductions in total and LDL cholesterol, resulting in a reduction in heart attack and cardiovascular death. Another important combination drug is aspirin, which has been shown to decrease the risk of outlook heart attacks in patients who have previously had a heart attack. Aspirin seems to work by reducing the stickiness of platelets, making them less likely to form clots. Aspirin produces reversible antibodies that can prevent primary and secondary heart disease. It may also reduce the risk of ischemic complications. The main responsibility of my work is the treatment of heart disease, and making recommendations. Numerous data suggest that combination therapy may provide better treatment outcomes compared to monotherapy. The polycarp was developed as a tablet containing metoprolol succinate, hydrochlorothiazide, simvastatin, and aspirin for major cardiovascular events. Several clinical studies have shown it to be efficient in lowering blood pressure, LDL cholesterol, and cardiovascular events.[3,4] This combination will maintain the safety and effectiveness of its parent compound. It can be used to target a wide range of people with high blood pressure as well as other risk factors from the combination, varying from dose to dose. The Indian Polycarp Study (TIPS) found that when a single drug was on, the combination drug was roughly as efficient as a single pill with no added adverse or side effects. Research Indian Polycarp has reduced the risk of cardiovascular disease, such as lowering blood pressure, heart rate, and blood lipids and reducing platelet viscosity. Mini tablet cap technology can reduce heart disease by more than 80% in healthy people. Four ingredient changes cost more than a month in a pill. The combined dose is estimated to be less than when the drug is taken alone. Reducing the burden of patients taking more than one drug positively affects the liver.[5] A person suffering from high blood pressure, diabetes, and heart disease should take 10 tablets daily to control many things. He said that taking multiple pills each day is expensive and tiring. I usually only include things I've already received, plus all expenses. Some of these drugs remind me of how uncomfortable I am still.[6,7]

This study aims to develop mini tablet cap technology with different components metoprolol succinate, hydrochlorothiazide, simvastatin, and aspirin. To form two bi-layer tablets, one of which is metoprolol succinate and hydrochlorothiazide, the polymers used are guar gum, xanthan gum, and HPMC K100, metoprolol succinate is the target of the gut, another mini bi-layer tablet is aspirin and simvastatin. The polymer material is HPMC K100 to reduce gastric release and drug release, and simvastatin for immediate release. Here, two mini bi-layer tablets are firmly fixed in a "00" size capsule. One of the mini bi-layer tablets contains simvastatin and aspirin, and the other contains hydrochlorothiazide and metoprolol. In this formulation, simvastatin and hydrochlorothiazide are immediate-release formulations, aspirin targets the stomach, and metoprolol is a controlled-release formulation.[8,9]

MATERIALS AND METHODS

Materials

As active ingredients metoprolol succinate, hydrochlorothiazide, simvastatin, aspirin purchased from Yarrow Chemicals, Mumbai; bigrade microcrystalline cellulose (MCC), used as a diluent, Avicel PH 101 and PH102; polyvinylpyrrolidone (PVP) was used as 0; HPMCK100 ethyl cellulose (EC100 cps) was used as the polymer releasing agent; and isopropanol SD as a granulation liquid. Pure chemicals. Personal. Ltd., Chennai. All components not used in this work are professional grade. HPLC grade dichloromethane was purchased from Anil Scientific, Vijayawada.

METHODS

Formulation Development of Mini Tablet Cap Technology

Step 1: Preparation of metoprolol succinate granules

Metoprolol mini tablet were manufactured by wet granulation. In the composition of formulation, guar gum, xanthan gum, and HPMC were sieved separately (<250 mm) to 100 and mixed with metoprolol and PVP. The powder is mixed with 5% powder and granulated. PVPK 30. Use isopropanol: water (1:1) as a granulating agent no. 10 nets. The product was dried at 50°C for 1 hour. Omit the dry granules for #1. Sift until 14 repetitions of small, weigh granules equal to 50 mg of drug and finally compact with a 6.5 mm tool. The formulation of the various samples selected in this study is shown in Table 1.[10]

Step 2: Preparation of aspirin granules

Table I provides a summary of the different formulations used in this study. In all formulations, HPMC K 15 is sieved separately (<250 mm) and mixed with aspirin (<150 mm) and PVP (<250 mm). The powder is mixed with isopropanol: water (1:1) as a granulating agent and granulated. Strain the moisture through a sieve and dry the pellet at 50°C for 2 hours no. 10 nets. The product was dried at 50°C for 1-hour. Omit the dry granules for #1. 14 Sieve once more to produce granules of the same size and weight equal to 75 mg of the drug, and finally push with a 6.5 mm tool.

Step 3: Preparation of hydrochlorothiazide granules

Crospovidone croscarmellose and SSG were sieved separately and mixed with hydrochlorothiazide, starch, and MCC in all formulations. The powder was mixed with isopropanol: water (1:1) and granulated using isopropanol: water (1:1) as a granulating agent. Strain the wet one through a sieve and dry

the pellets 50°C for 30 minutes no. 10 sieves. The product was dried at 50°C for 1 hour. Dried granules no. sieve again until 14 small sizes, weigh equal to 12.5 mg of the drug, and finally compact With 6.5 mm equipment.

Step 4: Preparation of simvastatin granules

The composition of the various preparations used in the study is shown in Tables VIII, IX, and X. All preparations contained crospovidone, croscarmellose, and SSG were sieved separately (<250 mm) and simvastatin (<150 mm) and starch mixed with MCC. (<250 mm). The powder was mixed and granulated with isopropanol used as a granulating agent. Strain the wet through a sieve and dry the pellets at 50°C for 30 minutes no. 10 nets. The product was dried at 50°C for 1 hour. Sieve the #14 dried granules again until the drug is small in size and weight of 10 mg drug, and finally compact with a 6.5 mm device

Step 5; Preparation of bi-layer tablets

Pre compression of SR granules & addition of IR granules and compression bilayer tablets were compressed into one layer of metoprolol succinate and the other layer of hydrochlorothiazide using a 7 mm concave tool on a 16-unit stationary rotary tablet punching machine. The tablets are formed into bilayer tablets using metoprolol succinate and hydrochlorothiazide granules. In this case, the granules of metoprolol succinate are first inserted into the mold cavity and slightly pre-pressed so that the distribution of the layers is uniform after the addition of the granules of hydrochlorothiazide and the final compaction. A second bilayer tablet was placed into one layer for aspirin only and the other layer for simvastatin using a 7 mm concave device on 16 fixed tablet staplers. The tablet is coated in a two-layer tablet using aspirin and simvastatin granules. Here, the aspirin granules first enter the mold cavity and are slightly pre-compressed to distribute the layer evenly. Simvastatin granules are then added and final compaction is carried out.

Step 6: Development of mini tablet cap technology

The above two mini bi-layer tablets are fixed properly in a "00" size capsule. A bi-layer tablet contains simvastatin and aspirin, and the other contains hydrochlorothiazide and metoprolol succinate. In this formulation, simvastatin and hydrochlorothiazide immediately release forms, aspirin is targeted at the intestine, and metoprolol is a control release dosage form (Figure 1).

Figure 1: Mini tablet cap technology containing minitablets filled in capsule size"00"

Table 1: Composition of optimized formulation of polycarp with two mini bi-layer tablets

Bilayer Tablet 1			
Sustained Release Metoprolol Succinate		*Immediate Release Hydrochlorthiazide*	
Ingredients	Quantity (Mg)	Ingredients	Quantity (Mg)
Metoprolol succinate	50	Drug-CD complex eq.12.5 mg	12.5
Guar gum	150	MCC	22.5
Lactose	--	Starch	39.5
PVP	10	SSG	6
Magnesium stearate	2.5	Isopropyl alcohol: water	QS
Talc	2.5	Mg.stearate	0.5
		Talc	0.5

Bilayer Tablet 2			
Sustained Release Tablet Aspirin		*Immediate Release Simvastatin*	
Ingredients	Quantity (Mg)	Ingredients	Quantity (Mg)
Aspirin	75	Drug-CD complex eq.10 mg	10
HPMC K100	60%	MCC	22.5
Lactose	-----	Starch	42
Magnesium stearate	2.5	Crosscarmellose	6
Talc	2.5	BHA	0.004
		Isopropyl alcohol	Q.S
		Mg.stearate	0.5
		Talc	0.5

Analytical Method for Polycp Mini Tablets Method for Assay

Preparation of sample solution

Crush the tablets and transfer the powder equivalent to 20 mg of asprin, 2.5 mg of simvastatin, 12.5 mg of HCTZ, and 3.5 mg of metoprolol into a 250 mL volumetric flask. Add 175 mL of solvent and sonicate for 30 minutes with continuous shaking. Allow the solution to settle down filter through 0.45 µ nylon membrane filter.

Chromatographic condition

Column: Zodiac C18, 50 x 4.6 mm, 5 µm or equivalent
Wavelength: 228 nm
Injection Volume: 20 µL
Column Temp: Ambient
Flow rate: 1.0 mL/minute
Retention time: Metoprolol: 3.3–3.5 minutes
HCTZ: 3.5–3.8 minutes
Aspirin: 4.5–5.0 minutes
Simvastatin: 8.8–9.3 minutes

Preparation of Diluent

Mix water and acetonitrile in a ratio of 30:70

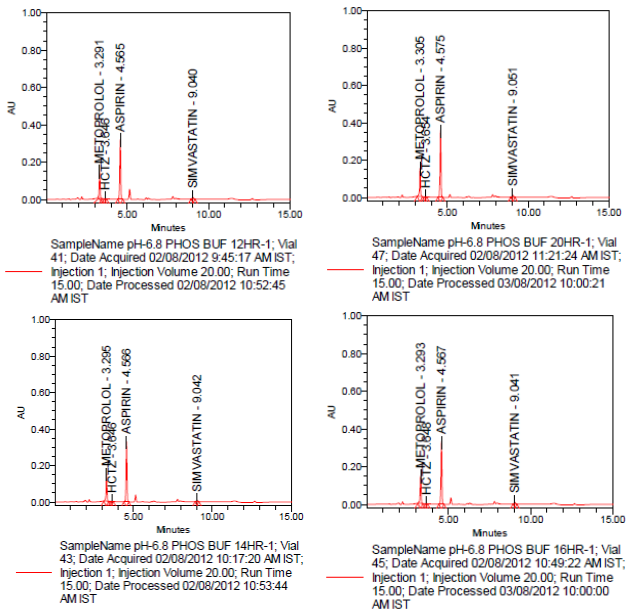

Figure 2: HPLC- Chromatogram graphs of mini tablet cap technology

Procedure

Inject equal volumes of blank (diluent), standard solution (5 times), and sample solution (twice) separately and measure the number of areas for the main peaks due to the respective peaks shown in Figure 2.

Evaluation Studies

Method for dissolution

Dissolution experiments were conducted using the USPXXI pallet method (Apparatus II). The mixing speed is 100 rpm. Minitablets was evaluated by performing *in-vitro* drug release studies in (PH 1.2) for 2 hours followed by an additional 24 hours at pH 6.8. Samples were taken at the specified time, and after the required dilution, the drug content was estimated by the RP-HPLC method for single drug prediction and the HPLC method for mini tablets drug search.

Infrared spectral studies

Using a Jasco FTIR spectrophotometer and the KBr palette approach (1:100) at a resolution rate of 4 cm^{-1}, IR spectra for the optimal closure of mini tablets with excipients and pure medicines were investigated. The spectrum and transmission mode were merged in the wave number range of 400 to 4000 cm^{-1}.

Pre-compression studies

Angle, bulk density (BD), tapped density, and Carr index were used to assess the flow characteristics of the lubricated granules. Except for CI and HR, all parameters were conducted out in three times (n = 3), and the data were articulated as (standard deviation mean). From the mean of BD and TD, CI and HR were computed.[11]

Post-compression Studies

Evaluate the properties of mini tablets after compression, such as thickness (mm), hardness (kg/cm^2), friability, and mass change. In the test, weigh a small tablet of the same amount of drug, transfer it to 100 mL of water: methanol, and sonicate for 15 minutes.[11]

Optimization studies

The concentration of HPMCK100, ethyl cellulose, and super disintegrating agents on mini tablets was studied using the one factor at a time method, and the vital quality control tests like the drug release profiles of simvastatin and hydrochlorothiazide for immediate release and metoprolol succinate and asprin drug product for sustained release in pH 1.2 and 6.8 phosphate buffer were measured to assess the formulation attributes. The following is the rationale for the formulation attributes chosen. An organic acid known as a super disintegrating agent functions as a bilayer separator reduces drug interactions approximately the active ingredients in the product, and increases the drug substance's stability. Therefore, a vital formulation attribute called the sustained released and immediate release tile lag period was chosen and researched.[12,13]

RESULTS AND DISCUSSION

Pre-compression research the flow characteristics of the lubricated blend findings presented in (Table 2) are unaffected by changes in the formulation attribute concentrations. Since all of the batches that were conducted had free flow and a high compressibility index, their lubricated blends were all suited for compression.

Post-compression Studies

The crushing force, friability, thickness, and mass variation of core mini bi-layer tablets as well as the results provided in (Table 3) were the compression qualities of these products, and the recommended alterations to formulation attributes had no effect on any of them. The optimization batches, the formulation crushing force was high, coming in at 1.13 x 0.05 kg/cm^2. This might be because the binder is so highly concentrated (PVP K30 is 11.93 mg/unit). To the pharmacopeia's satisfaction, all of the results were deemed to be satisfactory and to have fulfilled the limit criteria as per to regulatory specifications. The results are revealed in Table 3.

FTIR Study of Mini Bi-layer Tablet Cap

The FTIR spectra were analyzed, and it was found that the drug and its formulation had comparable distinctive peaks with little variation. As can be seen in Figure 3, there does not appear to have been any chemical interaction between the excipients and the medications used.

In-vitro Dissolution Studies

The mini Tablet cap technology of the improved formulation reveals 98% drug release of metoprolol succinate in 16 hours, 99% drug release of hydrochlorothiazide in 20 minutes, 82% drug release of aspirin in 24 hours, and 53% drug release of simvastatin in 15 minutes. According to the aforementioned research, the release rate was the same for formulations of both individual tablets and mini Tablet caps. Metoprolol succinate granules prepared with guar gum, xanthan gum, and HPMC K 100 in different ratios, among all these formulations, M-4

Table 2: Results of pre-compression studies on different active pharmaceutical ingredients

API	*Angle of repose(θ)*	*Bulk density (g/mL)*	*Tapped density (g/mL)*	*Compressibility index (%)*	*Hausner's ratio*	*Drug content (%)*	*Melting point*
Metoprolol succinate	24.5 ± 0.73	0.286 ± 0.02	0.321 ± 0.02	27.15	1.37	99.9	136+2
Hydro chlorothiazide	25.5 ± 0.63	0.288 ± 0.04	0.325 ± 0.02	23.9	1.52	98.7	274+2
Aspirin	24.6 ± 0.34	0.287 ± 0.11	0.324 ± 0.02	24.7	1.43	97	135+2
simvastatin	25.2 ± 0.52	0.291 ± 0.07	0.326 ± 0.02	24.5	1.35	98	130+2

*All the tests were conducted in three times (n=3) and the values are articulated as (Mean ± SD)

Table 3: Results of post-compressed studies on core bi-layer tablet

Formulation	*Weight variation (mg)*	*Thickness*	*Hardness (kg/cm^2)*	*Friability (%)*	*Disintegration (min)*	*Drug content (%)*
1st bilayer tablet	315 + 0.98	3.5	+ 0.5 5.0 ± 1.02	0.78 ± 0.01	I.R-10 seconds	99.2
					S.R-3 minutes	99.3
2nd bilayer tablet	270 + 0.87	3.3	+ 0.5 5.0 ± 1.02	0.85 ± 0.01	I.R-8 seconds	98.9
					S.R-4 minutes	99.9

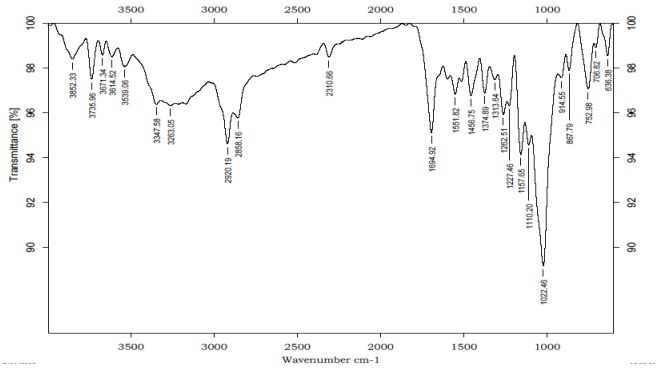

Figure 3: FTIR spectra of mini bi-layer tablet cap

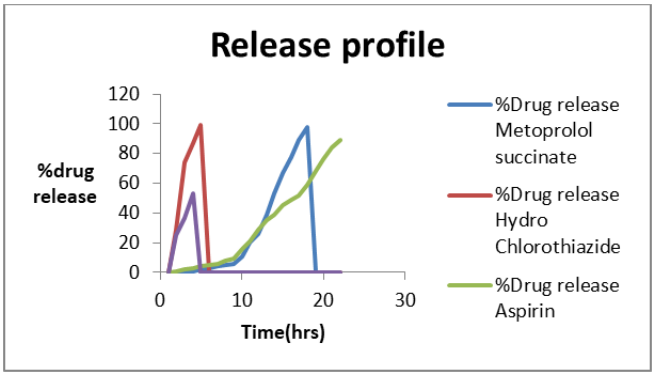

Figure 4: Comparative *in-vitro* dissolution profiles of mini tablet cap technology

(drug: guar gum1:3) shows sustained release for 16 hours. The capability of the selected gums to prolong the drug release is as follows: Guar gum, HPMC K100, and xanthan gum aspirin granules prepared with HPMC k15 in different ratios amongst all these optimized formulations (60%HPMC K100) shows the maximum amount of the drug released in duodenum up to 24 hours. Hydrochlorothiazide granules prepared with crospovidone, croscarmellose, and SSG in different ratios, among all these formulations, H-3 (6%crosspovidone) shows 98% of drug release within 20 minutes. The HPLC approach was the most effective way to estimate the medication from a mini tablet cap technology simultaneously is shown in (Figure 4). The drug kinetic release study was evaluated using Higuchi kinetics and Peppas drug release. The drug release mechanism follows Peppas, which was indicated to have a higher correlation value compared to the Higuchi equation.[14,15]

CONCLUSION

The design and development of a mini-tablet cap technology for the treatment of cardiovascular disorders were the goals of the current study. According to existing research material, monotherapy does not work well for cardiovascular illnesses. A variety of effective medications are needed to treat it. Therefore, the drugs chosen were aspirin, simvastatin, metoprolol succinate, and hydrochlorothiazide. In one capsule, the cap contains 75 mg of aspirin, 10 mg of simvastatin, 50 mg of metoprolol succinate, and 5 mg of hydrochlorothiazide. I chose two mini bilayer tablets fastened in a capsule to accomplish our goal; this technique is known as mini-tablet cap technology. Avoid heart attacks and strokes with a low-cost four-in-one capsule. The mini-tablet cap technology is one of the best dosage forms to treat cardiovascular diseases. It was reported that the combination of these four drugs reduces mortality by 83% in high-risk patients with heart disease, hypertension, diabetes, and obesity.

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