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Effect of viscosity of hydrophilic coating polymer on lag time of atenolol pulsatile press coated tablets

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Abstract
A method for the development of press coated tablet of atenolol for pulsatile delivery was investigated for chronotherapy of hypertension. Effect of viscosity of Hydroxypropylcellulose (HPC) on pulsatile release of atenlol was studied by press coating atenolol core tablet using different viscosity grade HPC and varying coat weight. L-HPC, M-HPC and H-HPC viscosity garde with 75, 100 and 150 mg coat weight were press coated over atenolol core tablets to delay release of atenolol. The batches, HP1-HP9, exhibited an increase in lag time in response to increase in viscosity and coat weight. Two of the batches HP5 and HP7 have shown a burst release of atenolol after 6.5 and 6.0 h lag time respectively, which is suitable for pulsatile drug delivery of atenolol for chronotherapy of hypertension.

Keywords: Atenolol; chronotherapy; pulsatile release; press coating; hydroxypropylcellulose; hypertension

1. Introduction

Chronobiology is the study of biological rhythms and their mechanisms.[1] Every biological rhythm has a periodicity of about 24 h. It is well known that circadian rhythms influence disease processes and physiological events. In case of cardiovascular diseases, several functions (e.g. blood pressure, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system (CVS) are subject to circadian rhythms. It has been reported that more shocks and heart attacks occur during morning hours.[2] The level of cortisol is higher in the morning hours, and its release is reported to decline gradually during the day.[3] Capillary resistance and vascular reactivity are higher in the morning and decreases latter in the day. Thus, Adjusting the administration of drug at an appropriate timing as predicted by circadian rhythm of disease could be advantageous in CVS disease control.[4] An emerging discipline, Chronotherapeutics is concerned with delivery of the drugs to acheive maximum concentration at the time of onset of symptoms that is predicted based on inherent activity of disease over a period of time.[5] In order to achieve the chronopharmaceutical design for the time controlled pulsatile type of colon targeted preparations, a formulation design should consider controlling the lag time is prior to the immediate release of drug.

Atenolol, a β-blocker, is prescribed widely in diverse cardiovascular diseases like hypertension, angina pectoris, arrhythmias and myocardial infarction. An oral administration of colon targeted pulsatile delivery of atenolol at bed time releasesing the drug after a desired lag time of about 6–6.5 h could be effective in controlling hypertension due to peak levels of cortisol, capillary resistance, platelet agreeability and vascular reactivity in the morning hours. The presented study investigates the effect of hydroxypropyl cellulose (HPC) on lag time of press coated pulsatile formulation of atenolol.

It was postulated that when the barrier layer was exposed to dissolution media, the HPC particles swell and erode, a process which was depends upon the viscosity grades and quantity of HPC, demonstrating that manipulation of both controls the lag time.[5] HPC has an ability to swell upon gellification once in contact with water. The gel becomes a viscous layer around a core, acting as a protective barrier to both the influx of water and the efflux of the drug in solution.[6] The HPC gel layer delays the atenolol release because of lengthening of the drug diffusion pathway. The rupturing or breaking time of the outer coat greatly depend upon the viscosity and coat weight of HPC.[7] Thus, in the present investigation, an attempt has been made to study the effect of viscosity and coat weight of HPC on lag time of time controlled pulsatile release tablets of atenolol.

2. Results and discussion

2.1. Spectrophotometric estimation of atenolol

Atenolol exhibited its maximum absorption at 225 nm and obeyed Beer's law with linear response in the range of 2.5-35 µg/mL. Calibration curves for atenolol in different solvents (methanol, 0.1 *N* HCl, phosphate buffer pH 6.8 and pH 7.4) were shown in **Figure 1**. All the curves have shown a linear regression of absorbance with regression coefficient near to 1.

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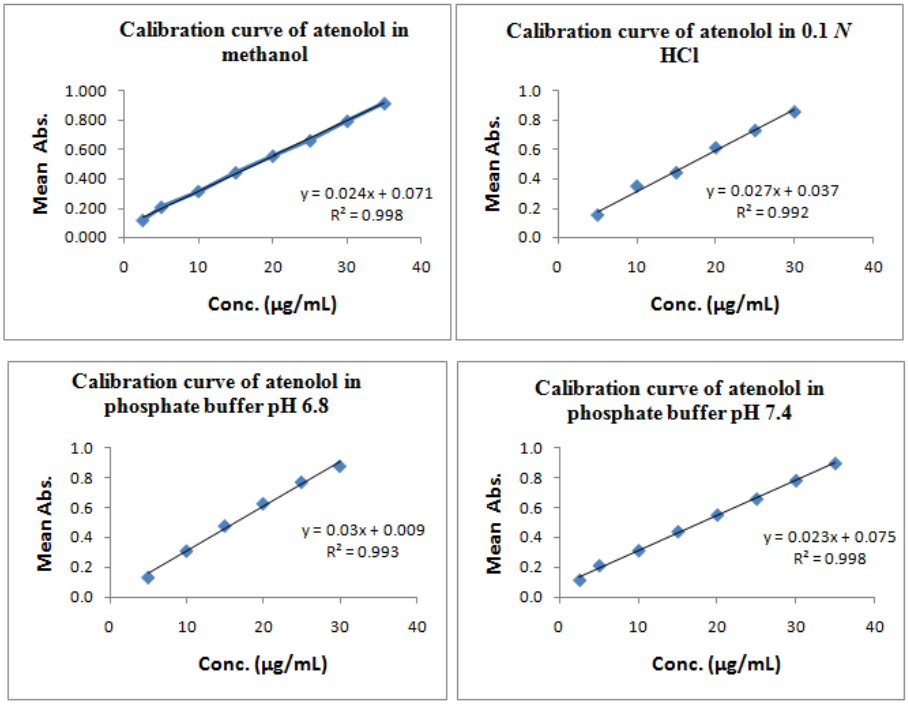

Figure 1: Calibration curves of atenolol in different solvent

2.2. Drug-Excipient compatibility study

2.2.1. Fourier transform infrared (FTIR) spectroscopy

Fourier transform infrared spectroscopy was used to analyze the pure sample powder of atenolol and powder of atenolol core tablet. FTIR spectra of these samples were shown in **Figure 2**. They were identical and the absorption bands due to functional groups of atenolol were present in all the spectra. Absorption band due to N-H stretch of $CO\text{-}NH_2$ group appeared at 3340 cm^{-1} and 3160 cm^{-1} in the both the spectra. The absorption band due to -C=O (amide I) and –N-C=O (amide II) stretch were located at 1625 cm^{-1} and 1500 cm^{-1} in spectra of both the samples and there was no shift in its position, a clear indication of drug-excipient compatibility. Other peaks due to =C-H stretching (2940 cm^{-1}), $-CH(CH_3)_2$ (1383 cm^{-1} & 1170 cm^{-1}) and Ar-O-C (1390 cm^{-1} & 1235 cm^{-1}) were also present in both the spectra.[8] The FTIR spectra of the tested samples have shown the prominent characterizing peaks of pure atenolol confirming no chemical modification due to any drug-excipient interaction at the molecular level.

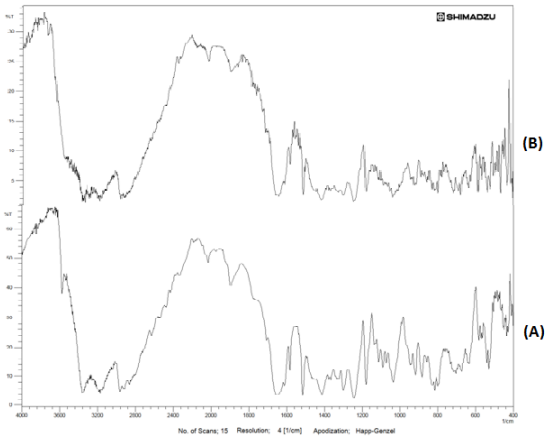

Figure 2. FTIR spectra of: pure sample powder of atenolol (A) and powder of atenolol core tablet (B)

2.2.2. Differential Scanning Calorimetry (DSC)

DSC thermographs of pure sample powder of atenolol and powder of atenolol core tablet has shown a sharp exothermic peak (Tm) at 156.11 °C and 156.21 °C respectively, which corresponding to melting point of atenolol (154 °C to 156 °C)**.8, 9** Melting exotherm not appreciably change in powder of atenolol core tablet as compared to atenolol pure sample. This observation confirmed the absence of any chemical interaction of drug with excipients of core tablet, further supporting the results of IR spectroscopy. The DSC results of pure sample powder of atenolol and powder of atenolol core tablet were shown in **Figure 3**.

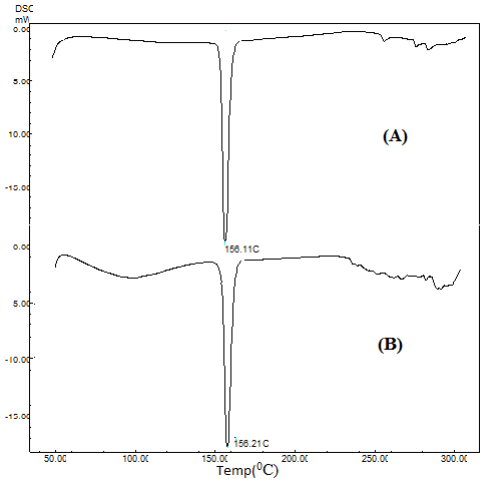

Figure 3. DSC thermographs of: pure sample powder of atenolol (A) and powder of atenolol core tablet (B)

2.3. Flow property study of powder blend

The bulk density, tapped density, angle of repose, hausner's ratio and carr's index of powder blend for atenolol core tablets are 0.280±0.03, 0.33±0.04, 29.74°±0.40, 1.178±0.12 and 15.15±0.65 respectively (**Table 1**). The results indicated that the powder blend

has good flow property and compressibility compared with pure sample powder of atenolol and suitable for direct compression method.

The angle of repose, hausner's ratio and carr's index of powder blend used for coating of core tablets were ranged from 28.72°±0.54 to 29.74°±0.25, 1.15±0.15 to 1.171±0.12 and 13.04±0.43 to 14.63±0.35 respectively as shown in **Table 1**. The values of pre-compression parameters indicated a good free flowing property and suitable for direct compression method.

Table 1. Flow property study for powder blends of various grades of HPC

Formulation Code	BD[a] (g/cm^3)	TD[a] (g/cm^3)	CI (%)[a]	HR (H_R) [a]	AoR (Θ) [a]
AT2	0.28 ±0.03	0.33 ±0.04	15.15 ±0.65	1.18 ±0.12	29.74° ±0.40
L - HPC	0.35 ±0.05	0.41 ±0.04	14.63 ±0.35	1.17 ±0.12	29.74° ±0.25
M –HPC	0.40 ±0.04	0.46 ±0.03	13.04 ±0.43	1.15 ±0.15	28.72° ±0.54
H - HPC	0.39 ±0.03	0.45 ±0.05	14.44 ±0.37	1.17 ±0.16	29.39° ±0.47

[a](mean± SD); BD-Bulk Density; TD-Tapped Density; CI-Carr's Index; HR-Hausner's Index; AoR-Angle of Repose

2.4. Post compression study of core tablets and press coated tablets

The data obtained from post-compression study of core and press coated tablets such as weight variation, hardness, friability, and drug content are shown in **Table 2**. The hardness of core tablets of atenolol was 3.25±0.15, indicated that core tablets had good crushing strength. The friability, drug content, weight variation and thickness of atenolol core tablets were 0.12±0.05%, 99.97±1.3%, 79.57±2.57 and 3.2±0.04 respectively, which indicated that atenolol core tablets passed the post compression study. Atenolol core tablets have shown disintegration time of 28±1.52 sec, which is important parameter for burst release after a 6 h lag time.

Table 2. Post-compression parameters of rupturable and erodible type press coated tablets

Formulation Code	H[a] (kg/cm^2)	F[a] (%)	DC[a] (%)	WV[a] (mg)	TT[a] (mm)
AT2	3.25 ±0.15	0.12 ±0.05	99.97 ±1.3	79.57 ±2.57	3.2 ±0.04
HP1	4.0 ±0.35	0.17 ±0.06	99.80 ±1.3	155.67 ±1.45	4.0 ±0.04
HP2	5.5 ±0.5	0.12 ±0.06	99.57 ±1.5	188.40 ±2.95	5.0 ±0.05
HP3	6.5 ±0.3	0.08 ±0.05	100.95 ±1.2	228.35 ±2.25	5.9 ±0.04
HP4	4.0 ±0.4	0.15 ±0.08	99.15 ±1.8	154.25 ±2.57	4.0 ±0.02
HP5	6.0 ±0.6	0.11 ±0.05	100.65 ±1.6	189.50 ±2.50	5.0 ±0.05
HP6	7.0 ±0.4	0.06 ±0.07	99.84 ±1.4	229.26 ±2.76	5.9 ±0.04
HP7	4.5 ±0.5	0.12 ±0.04	100.54 ±1.2	153.8 ±3.15	4.0 ±0.03
HP8	6.0 ±0.3	0.09 ±0.08	99.75 ±1.5	187.75 ±1.55	5.0 ±0.04
HP9	7.5 ±0.45	0.06 ±0.05	99.45 ±1.3	230.67 ±2.20	6.0 ±0.03

[a](mean± SD); H-Hardness; F-Friability; DC-Drug Content; Weight Variation; Tablet Thickness

In all press coated formulations, the hardness test indicated good mechanical strength. Hardness has ranged from 4.0-7.5 kg/cm^2. Friability was ranged from 0.06±0.05 to 0.17±0.06. Friability is less than 1% which indicated that tablets had good mechanical resistance. Drug content was found to be high (>99.15%). It was ranged from 99.15±1.8 to 100.95±1.2% and uniform in all tablet formulations. In weight variation test, twenty tablets were selected randomly and average weight was calculated. Then individual tablet was weighed and was compared with average weight. None of tablets showed more than 7.5% weight variation from average weight. So, all formulations pass the weight variation test as per Indian Pharmacopoeia, 2007. Tablet thickness varied from 4.0 to 6.0 mm.

2.4.1. Swelling study

Table 3 describes the percentage swelling ratio of different batches of press coated tablets (HP1-HP9). The study indicated that as the amount of HPC increases, the swelling of tablet increases. The batches from HP1-HP3 have shown complete disintegration within 0-1.5 h due to low viscosity of L-HPC.[5] But, as viscosity of HPC increases to medium level, it did not show any disintegration but started to show swelling. The percentage swelling of M-HPC coated tablets (HP4-HP6 batches) increases as the coat weight of M-HPC increases from 91.86±5.85 to 168.39±4.87. The higher viscosity grade of HPC (H-HPC) has shown high percentage of swelling (227.45±4.34%) with high coat weight.

Table 3. Lag time and % swelling index of atenolol press coated tablets

Formulation Code	Lag Time (h)	% Swelling Index
HP1	0	Disintegrated
HP2	1	Disintegrated
HP3	1.5	Disintegrated
HP4	5	91.86±5.85
HP5	6.5	135.64±6.57
HP6	8.5	168.39±4.87
HP7	6	127.69±3.96
HP8	8.5	179.37±5.53
HP9	11	227.45±4.34

2.4.2. *In vitro* dissolution study of atenolol press coated tablets

In time controlled press coated tablets, different batches (HP1-HP9) have shown a variable lag time depending on the concentration and viscosity grade of HPC in the outer coating layer. The press coated tablets showed a lag time before the drug release because the atenolol core tablets were completely surrounded by the polymer layer that prevented the release of drug from the core tablets. Burst release after a specific lag time occurred due to swelling and erosion of the outer hydrophilic HPC layer. When the polymer layer swelled adequately, it allowed sufficient dissolution medium to enter into it and reach the core tablet. The superdisintegrant in the core swelled extensively which exerts a pressure on the outer layer resulting in burst release of the drug.[10]

Figure 4 shows the dissolution profile of various press coated tablet batches (HP1-HP9). Press coated tablets (HP1-HP9) exhibited distinct lag time as given **Table 3**. It is possible to obtain lag time of 1-11 h using different HPC viscosity grades and coating weight (**Table 4**). The swelling and subsequent erosion of outer coating layer of HPC determines the lag time of atenolol press coated tablets. Formulations HP1-HP9 have shown an increase in lag time with increase in weight ratio of HPC because upon contact with dissolution medium HPC forms a gel like structure that delays the release of drug depending

on quantity of gel layer. The lag time should be longer with increase in HPC viscosity, because the dissolution rate or erosion rate of the HPC polymer would be delayed as molecular weight of HPC polymer increases (Shinde and Mayee, 2012).[11]

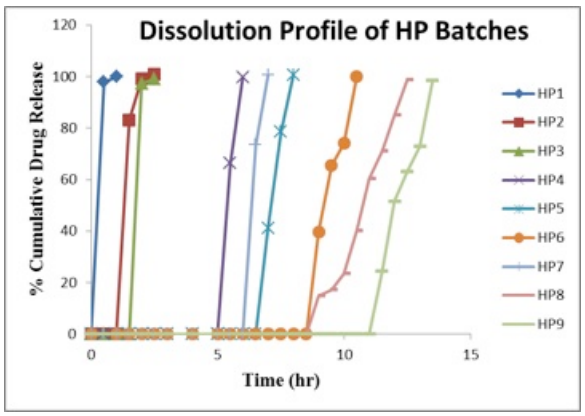

Figure 4. Dissolution profile of atenolol press coated tablets

Table 4. Formulations of press coated tablets of atenolol

Formulation code	Core tablet	Grade of HPC	Coat Weight (mg)
HP1	A2	L-HPC	75
HP2	A2	L-HPC	100
HP3	A2	L-HPC	150
HP4	A2	M-HPC	75
HP5	A2	M-HPC	100
HP6	A2	M-HPC	150
HP7	A2	H-HPC	75
HP8	A2	H-HPC	100
HP9	A2	H-HPC	150

The dissolution profile of batche HP1 has shown the rapid drug release within 30 min as 75 mg coat weight of L-HPC is insufficient to retard the release of atenolol. The dissolution study of batches H2 and H3 as shown in **Figure 4** revealed that even at higher concentrations of L-HPC, the drug release was retarded only for about 1-1.5 h respectively, as low viscosity grade of HPC was not found suitable. Moreover L-HPC is a disintegrant and had been used to cause rapid disintegration of tablets.[5] Thus, a higher viscosity grade of HPC was used in further trials.

The lag time of drug release was delayed with the increase of the viscosity grade and coat weight of HPC and the release rate was also decreased. The dissolution profile of batches H4-H6 have shown the lag time of 5, 6.5 and 8.5 h respectively. As shown in **Figure 4**, the higher viscosity grade of HPC (M-HPC) was found to be sufficient to design the desired lag time to release the drug at the scheduled time and then release most of the drug within a short time period in the colon. Formulation HP5 exhibited the lag time of 6.5 h, after that it released drug by bursting effect as pressure generated in core tablet is enough to break the outer coating layer of M-HPC after some erosion of outer gel layer of M-HPC.[11] It has also shown that lag time decreases with coat weight of M-HPC. M-HPC swells due to absorption of water, which delayed the release of drug, thus as the coat weight of M-HPC was increased, lag time increases. It showed that Formulation HP6 having coat weight of M-HPC at 150 mg, showed lag time of 8.5 h.

If a higher viscosity grade of HPC (H-HPC) was used to prepare press coated atenolol tablet, than formulation HP7 having lower coat weight of H-HPC (75 mg), is sufficient to achieve desired lag time of 6 h. But, formulations HP8 and HP9 containing higher coat weight of H-HPC was not suitable for this purpose, as it showed the delayed lag time of 8.5 and 11 h respectively due to formation of stable gel layer of H-HPC around atenolol core tablets for a long period of time. As shown in **Figure 4**, dissolution profile of formulation HP8 and HP9 showed the initial slow drug release prior breakage of gel layer of H-HPC, because as dissolution medium penetrate into the coating layer and it hydrates the core, but due to tight gelled structure of H-HPC around core tablet, some drug is eject out through gel layer by diffusion mechanism. When internal pressure was build inside the core is enough to break the gel layer of H-HPC, rapid drug release was observed at later stage.[12]

Results of *in vitro* dissolution study of atenolol press coated tablets were shown in **Table 5**. The two batches HP5 and HP7 have achieved a burst release after 6.5 and 6 h lag time respectively. Thus, the dosage forms can be taken at bedtime, so, that the content will be released in the morning hours, i.e., at the time of symptoms. The release of drug was rapid and complete after the lag time. Lag time was greatly affected by viscosity and coat weight of HPC.

3. Experimental

Materials and methods: Atenolol was obtained as a gift sample from Zydus Cadila Healthcare Ltd., Ahmedabad, India. Sodium starch glycolate IP was obtained as a gift sample from Maruti Chemicals, Ahmedabad, India. L-HPC, M-HPC, H-HPC were received as a gift sample from Nippon Soda Co. Ltd., Tokyo, Japan. Polyvinyl pyrollidone K 30 (PVP) (S. D. Fine Chemicals Ltd., Mumbai, India); microcrystalline cellulose, talcum powder, magnesium stearate and sodium hydroxide (Chemdyes Corporation, Rajkot, India); potassium dihydrogen phosphate (Merck Specialities Pvt. Ltd., Mumbai, India) and methanol (Ranbaxy Fine Chemicals Ltd., New Delhi, India) were purchased from respective vendors.

3.1. Evaluation of flow property of powder blends

Powder blends used for preparation of atenolol core tablets and press coated tablets were evaluated for flow property by measuring bulk density, tapped density, carr's index, hausner's ratio and angle of repose.

3.2. Preparation of atenolol core tablets

The core tablets of atenolol (A2) were prepared by direct compression method. An optimized core tablet was formulated using various concentrations of dry binder and super disintegrant as describe in **Table 6**. An accurately weighed quantity of atenolol, microcrystalline cellulose, polyvinyl pyrroloide (PVP K30) and sodium starch glycolate were passed through 40# sieve and mixed in a double cone blender for 15 min. Talc (2% w/w, 40#) was added into the blend and mixed for 10 min. that was followed by magnesium stearate (1% w/w, 40#) and continued for another 5 min. The resultant powder mixture was compressed into tablets (average tablet weight=80 mg) by 6 mm standard concave plain punches using rotary tableting machine (Hardik Engineering Works, Ahmedabad, India) and compression force was controlled to produce more than 3±0.5 kg/cm^2 tablet hardness. The prepared

Table 5. % cumulative drug release study of atenolol press coated tablets with HPC

Time (h)	HP1	HP2	HP3	HP4	HP5	HP6	HP7	HP8	HP9
0	0	0	0	0	0	0	0	0	0
0.5	97.75	0	0	0			0	0	0
1	99.87	0	0	0	0	0	0	0	0
1.5		83.14	0	0	0	0	0	0	0
2		98.96	97.25	0	0	0	0	0	0
2.5		100.84	99.12	0	0	0	0	0	0
3				0	0	0	0	0	0
4				0	0	0	0	0	0
5				0	0	0	0	0	0
5.5				66.43	0	0	0	0	0
6				99.64	0	0	0	0	0
6.5					0	0	73.41	0	0
7					41.25	0	100.42	0	0
7.5					78.46	0		0	0
8					100.48	0		0	0
8.5						0		0	0
9						39.67		14.88	0
9.5						65.35		17.21	0
10						74.00		23.47	0
10.5						99.99		40.37	0
11								60.33	0
11.5								71.08	24.4
12								85.01	51.55
12.5								98.83	63.20
13									72.80
13.5									98.51

atenolol core tablets were tested for weight variation, hardness, thickness, drug content, disintegration time, friability and *in vitro* dissolution study by standard methods.[12-14]

Table 6. Composition of atenolol core tablet

Ingredients	Quantity/tablet (mg)
Atenolol (API)	45 mg
Sodium Starch Glycolate (SSG) (5%)	4 mg
Polyvinyl pyrollidone K30 (PVP K30) (5%)	4 mg
Microcrystalline Cellulose (MCC)	24.6 mg
Talc (2%)	1.6 mg
Mg Stearate (1%)	0.8 mg
Total Weight	80 mg

3.3. Preliminary Trial Batches

As shown in **Table 7** preliminary trials batches of atenolol press coated tablets were prepared randomly using different viscosity grade and coat weight of HPC on trial and error basis to select the desired coat weight.

Table 7. Preliminary trail batches of various grades of HPC

Type of grade	Coat Weight (mg)	Lag time (h)
L-HPC	50	0
L-HPC	200	2
M-HPC	50	0
M-HPC	100	6.5
M-HPC	200	10
H-HPC	50	3
H-HPC	75	6
H-HPC	200	14

3.4. Preparation of atenolol press coated tablets

To study the effect of viscosity on the lag time of press coated colon targeted time release atenolol tablet, the core tablets were press coated with coating material containing various viscosity grades of HPC. The coat weight of various viscosity grades of HPC as decided from the preliminary trial batches (**Table 7**) were used for the compression coating shown in **Table 4**. An accurately weighed quantity of coating material, magnesium stearate (1% w/w) and talc (2% w/w) were passed through sieve no. 22 separately and blended using a mortar and pestle for 10 min. Coating material (43% w/w) was first placed into die cavity (internal diameter 9 mm). Then, the core tablet was carefully placed on it manually at the centre of the die. The remaining coating material (57% w/w) was added into the die and compressed around the core tablet by 9 mm standard concave plain punches using rotary tableting machine (Cadmach Machinery, Ahmedabad, India). Compression force was controlled to produce 5±0.5 kg/cm^2 tablet hardness. The prepared compression coated atenolol tablets were tested for weight variation, hardness, thickness, drug content, friability and *in vitro* dissolution study by standard methods.[15-18]

3.5. Spectrophotometric evaluation of atenolol core and press coated tablets

Atenolol was estimated by UV visible spectroscopy. Calibration curve of atenolol was prepared in different solvents (methanol, 0.1 *N* HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4). Accurately weighed 100 mg of atenolol was placed in 100 mL volumetric flask and dissolved in 100 mL of solvent. From this solution, 10 mL solution was withdrawn and further diluted to 100 mL to yield the standard stock solution of atenolol (100 µg/mL). From the stock solution; 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, 30.0 and 35.0 mL were withdrawn and diluted to 100 mL to yield concentration of 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, 30.0 and 35.0 µg/mL respectively. Absorbance of each dilution was measured at 225 nm using UV-Visible spectrophotometer (Thermo Scientific Evolution 201). Samples were analyzed in triplicate and the average values were used for plotting the graph of absorbance versus concentration (µg/mL). Regression analysis was done on each beer's plot using Microsoft excel.[8]

3.6. Drug-Excipient compatibility study

3.6.1. Fourier transform infrared spectroscopy

The FTIR spectra of pure sample powder of atenolol and powder of atenolol core tablet were recorded on a FTIR

spectrophotometer (Shimadzu, FTIR-8400S), in the wavelength region of 4000-400 cm^{-1} using KBr with sample concentration of about 1% w/w.

3.6.2. Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (DSC-60, shimadzu corporation, Japan) was used to monitor the thermal events during heating. The DSC was calibrated using indium (156.6±0.2 °C) and zinc (419.5±0.3 °C) standards. Samples of pure sample powder of atenolol and powder of atenolol core tablet weighing 2–3 mg were placed in an open aluminium pans and heated from 50 to 300 °C at a rate of 20 °C per min. Nitrogen was used as a purge gas at a flux rate of 50 mL/min. The onsets of the melting points were recorded using the software, Pyris from Perkin-Elmer.

3.7. Flow property study of powder blend

Flowability of powder blend used for preparation of atenolol core and press coated tablets was evaluated by determining angle of response, carr's consolidation index and hausner's ratio.

3.8. Post compression study of core tablets and press coated tablets

3.8.1. Weight Variation

Twenty tablets from each batch were individually weighed using electronic digital balance (Shimadzu BL-220H) and average weight was calculated. Individual weights of the tablets were compared with the average weight according to the official method in Indian Pharmacopoeia, 2007.[19, 20]

3.8.2. Hardness

Six tablets from each batch were selected and tested for tablet hardness using Monsanto hardness tester. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture that causes the tablet to break was recorded.[21]

3.8.3. Thickness

The thickness of ten tablets from each batch was determined using vernier calipers as per Indian Pharmacopoeia, 2007.[22]

3.8.4. Friability (F)

The friability of twenty tablets from each batch was determined using Roche friabilator (Indosati Scientific Lab. Equipments).[23, 24] This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. A pre-weighed sample (20 tablets) was placed in the friabilator and is subjected to 100 revolutions. Tablets were dedusted and reweighed. The % friability (F) was calculated using the formula given below:

$$F = \left(\frac{W_1 - W_2}{W_1} \right) x100$$

Where, W_1 is the initial weight of twenty tablets before the test and W_2 is the final weight of twenty tablets after the test

3.8.5. Drug content

For determination of drug content, ten tablets were crushed into powder and powder equivalent to 45 mg of atenolol was weighed and dissolved in methanol. It was then filtered through syringe filter (Axiva SFCA25X, 0.45 µm) and the filtrate was analyzed for atenolol content spectrophotometrically using UV-Visible spectrophotometer (Thermo Scientific Evolution 201) at 225 nm with methanol as blank.[25]

3.8.6. Swelling studies

One tablet from each batch of press coated formulation was randomly selected, weighed individually (W_1) and placed separately in petridishes having 8.5 cm diameter containing 20 mL of phosphate buffer (pH 7.4). After 6 h, the tablets were carefully removed from petridishes and excess water was removed using filter paper. The swollen tablets were reweighed (W_2) and swelling index (SI) expressed in percentage for each tablet was calculated using the formula given below.[26, 27]

$$SI = \frac{(W_2 - W_1)}{W_1} x100$$

Where, W_1 is the initial weight of each tablet before test, W2 is the final weight of each tablet after test

3.8.7. Disintegration test

Six tablets from each batch were placed in the glass tube of disintegration test apparatus (Indosati Scientific Lab. Equipments) containing 900 mL of water maintained at a temperature of 37±1 °C and disintegration time of core tablets was determined according to official method in Indian Pharmacopoeia, 2007.[2, 28]

3.8.8. *In vitro* drug release study of atenolol press-coated tablets

In vitro drug release studies were carried out using USP Type II dissolution apparatus (Electrolab, TDT-08L) in a 900 mL of dissolution media at a temperature of 37±1 °C at 100 rpm. In order to simulate the pH changes along the GI tract, multimedia dissolution studies were performed. Three dissolution media with pH 1.2, 6.8 and 7.4 were sequentially used. Initially dissolution study was performed using 0.1 *N* HCl (pH 1.2) as dissolution medium for 2 h (since the average gastric emptying time is 2 h). Then the dissolution medium was replaced with phosphate buffer pH 6.8 and the study was continued for another 3 h (average small intestinal transit time is 3 h). After 3 h, the dissolution medium was again replaced with phosphate buffer pH 7.4 and the study continued for subsequent hours. At regular time intervals, a 10 mL of portion of sample was withdrawn for content analysis and same amount of fresh medium has been replaced. Samples withdrawn were suitably diluted and filtered through syringe filter (Axiva SFCA25X, 0.45µm). The amount of drug released was estimated spectrophotometrically using UV-Visible spectrophotometer (Thermo Scientific Evolution 201) at 225 nm. All studies were carried out in triplicates.[25, 27, 29] The time for which the tablet does not show any release of the drug is known as its lag time. The lag time can be determined from the dissolution profile of the tablet.

Abbreviations

HPC-hydroxy propylcellulose; **L-HPC**-low molecular weight HPC; **M-HPC**-Medium molecular weight HPC; **H-HPC**-high molecular weight HPC; **SI**-swelling index

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