ORIGINAL ARTICLE

Formulation and Evaluation of Chronomodulated Press-coated Tablets of Tapentadol HCl

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Abstract

Aim: Press-coated tablets of Tapentadol HCl are proposed to achieve the release of drug after a programmable period of time. It is intended to be used mainly in the therapy of those diseases and symptoms which depend on circadian rhythms like many pain conditions. **Methods:** A core formulation containing Tapentadol hydrochloride as model drug is coated by compression with different polymeric barrier layers (press-coated systems) in different weight ratios. The core serves as a reservoir, and the release-controlling layer protect the core from the environment, e.g., water, acidic pH, and enzymes until the drug is released after a predetermined lag phase. The coatings can erode/dissolve, rupture or alter their permeability at the required time. The shell formulations tested contained erodible polymers. The dissolution profiles of uncoated cores and press-coated devices were compared. The coating is expected to prevent drug release from the core until the polymeric shell is completely eroded or swollen. Nine formulations were prepared and evaluated for various parameters. **Results:** Formulation F3, F4, and F6 possessed good lag time 4–4.5 h and showed pulsatile drug delivery pattern. Except for the time-lag, the release kinetics of the drug contained in the core were not significantly influenced by the presence of the erodible barrier but can be widely be modulated using a swellable polymeric shell. **Conclusion:** Results of the study indicated that floating - press-coated based pulsatile release formulations are suitable for Tapentadol hydrochloride.

Key words: Chronomodulated, erodible, lag-phase, press-coated, pulsatile, swellable

INTRODUCTION

The goal of drug delivery research is to develop formulations that meet therapeutic needs relating to particular pathological conditions.[1] Research in chronotherapeutics field has demonstrated the importance of biological rhythms in drug therapy. According to this, if the symptoms of disease display circadian variations, drug release should also follow time. Variations in physiological and pathophysiological functions in time and need for variations of drug plasma concentration have brought a new approach to the development of drug delivery systems - chronopharmaceutical drug delivery.[2]

In chronopharmacotherapy, drug administration is synchronized with circadian rhythms.[3] If the peak of symptoms occurs at daytime, a conventional dosage forms can be administrated just before the symptoms are worsening. If symptoms of the disease became worse during the night or in the early morning, the timing of drug administration and nature of the drug delivery system needs careful consideration. In this case, modified-release dosage forms must be used.[4]

These systems are beneficial for the drugs having chronopharmacological behavior (where night time dosing is required), first-pass effect and having a specific site of absorption in gastrointestinal tract.[5]

Conventional once daily extended-release drugs usually sustain drug concentration over the 24 h dosing. Conventional

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slow-release (SR) medications are formulated to ensure a near-constant drug concentration.[6,7] From the viewpoint of therapeutic optimization, maintaining a constant blood level for a drug in the human body is questionable. Long-term constant drug concentration exposed in blood and tissues may induce many problems such as tolerance of drug and activation of physiological system.[8] Recently, chronotherapy has been extensively applied in clinical therapy by modulating the dosing regimen of drug administration according to physiological needs.[9] Chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules and a drug-delivery system to synchronize drug concentrations to rhythms in disease activity. Diseases wherein patient determined disease steps are promising to include asthma, peptic ulcer, cardiovascular diseases, arthritis, and hypercholesterolemia.[10] The pathophysiology of arthritis and patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis have pain that usually peaks in the morning and decreases throughout the day.[11]

In the present work, we examined the drug Tapentadol hydrochloride, 3-[(1R, 2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl] phenol hydrochloride is a novel analgesic agent with two mechanisms of action within the same molecule: Agonist activity at the μ opioid receptor and norepinephrine reuptake inhibition.[12-14] Both immediate release and extended release formulations of Tapentadol are available and appear to provide analgesia in acute and chronic pain states similar to oxycodone or morphine. Tapentadol is available in both immediate and extended release dosage forms as Nucynta ER, Nucynta™ CR, Palexia, Palexia Depot, Palexia Retard, and Palexia SR. Tapentadol HCl is a "Class-I" drug according to Bio-pharmaceutics Classification System, possessing both high solubility and high permeability absorption characteristics[15] but it is extensively metabolized by first-pass metabolism and has biological half-life of 4–5 h, its systemic bioavailability of 32% is achieved after single dose.[13] It also requires dosing every 5 h to maintain optimal relief of chronic pain. Tapentadol HCl is used in the management of moderate to severe chronic pain and neuropathic pain. Many of which address early morning surges.

MATERIALS AND METHODS

Tapentadol hydrochloride was procured from MSN Labs Hyd. L-hydroxypropyl cellulose (HPC) sample was procured from Agilent Pharma. Other chemicals were purchased from HiMedia, Mumbai, and were of analytical grade. Polyvinylpyrrolidone (PVP), microcrystalline cellulose, and lactose were obtained from SD Fine Chem Ltd., Mumbai.

Drug excipients compatibility study

The pure drug, mixture of optimized formulation, physical mixture of coating material and drug, and core tablet mixture were subjected to IR spectroscopy using Fourier transform-infrared (FT-IR) spectrophotometer (IR Affinity-1, Shimadzu). Their spectra were obtained over the wavenumber range of 4000–400/cm.

Preparation of core tablet containing drug

The core tablets of Tapentadol HCl were prepared by direct compression technique. Different core tablets were prepared, and the best composition was chosen based on evaluation parameters for this study. The selected core tablets contained 50 mg of the drug, 13 mg of Lactose, 10 mg of Polyox 303 WSR, and 5 mg PVP and 2 mg of magnesium stearate.

At First, mentioned quantities of drug, Polyox and PVP were mixed thoroughly. Lactose and magnesium stearate was added and mixed uniformly. Powder was compressed into 5 mm flat tablets with use of a single station tablet machine (Remi Mini Press, Ahmedabad, India). The core tablets were evaluated for hardness, thickness, content uniformity, friability, and disintegration.

Preparation of compression-coated tablets

On compliance with the above-mentioned tests, the core tablets were compression coated with different weight ratios (w/w) of the hydrophobic erodible polymer blend. Initially, 50% of the coat powder (hydrophobic erodible polymer blend) was placed in the die cavity then, the core tablet was carefully positioned at the center of the die cavity which was filled with the remainder of the coat powder. It was then compressed around the core tablet using 10 mm round, flat, plain punches at a pressure of 175 kg/cm^2. Formulations of press-coated tablet were shown in Table 1. The press-coated tablets were further evaluated for hardness, thickness, content uniformity, friability, and disintegration, and lag time.

Drug content of core tablet

The core tablet was finely powdered, and quantity of the powder equivalent to 10 mg of drug was accurately weighed and transferred to a volumetric flask containing 100 ml of 0.1N HCl and mixed thoroughly. One milliliter of filtrate with suitable dilution was estimated for drug content at 272 nm using double beam spectrophotometer (Shimadzu Corporation, Japan, UV-1700).

Characterization of core and press coated tablet

All the pre- and post-compression parameters were evaluated for both core and press-coated tablets as per the pharmacopeial standards. The evaluated pre-compression parameters were the angle of repose, bulk and tapped density, compressibility index (Carr's index), and Hausner's ratio. The post-compression parameters evaluated for both core and press-coated tablets were thickness, hardness, and uniformity

Table 1: Formulations of press-coated tablets

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core tablet (mg)									
Drug	50	50	50	50	50	50	50	50	50
Polyox	10	10	10	10	10	10	10	10	10
Lactose	15	15	15	15	15	15	15	15	15
PVP	5	5	5	5	5	5	5	5	5
Mg St.	2	2	2	2	2	2	2	2	2
Coat powder (mg × 2)									
EC	50	-	-	75	-	-	100	-	-
E S100	-	50	-	-	75	-	-	100	-
L-HPC	-	-	50	-	-	75	-	-	100
MCC	10	10	10	10	10	10	10	10	10
HPMC K100	15	15	15	15	15	15	15	15	15
$NaHCO_3$	10	10	10	10	10	10	10	10	10

PVP: Polyvinylpyrrolidone, HPMC: Hydroxypropylmethyl cellulose, HPC: Hydroxypropyl cellulose

of weight. The core tablets were specifically evaluated for disintegration time and drug content (assay) whereas the press-coated tablets were assessed for percentage friability. All tablet parameters were complied with pharmacopeial standards, and the results are expressed as a mean ± standard deviation, given in tables.

Dissolution study performed for core tablets

Drug dissolution rate was studied using USP XXIII dissolution test (USP type-II Apparatus, Lab India DS 8000). The dissolution bath was maintained at 37°C ± 0.5°C at 50 rotations per minute. Samples of 5 ml were withdrawn from dissolution medium at pre-determined intervals and replaced with the same volume of fresh dissolution media. For core tablets, dissolution study was carried out for 8 h. For press-coated tablets, it was carried out for 12 h. The samples were assayed for drug content by measuring the absorbance at 276 nm using UV-visible spectrophotometer (PG Analyticals-T60).

RESULTS AND DISCUSSION

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of excipients used in the formulation. It was found that there was no chemical interaction between the drug and the excipients used as; there were no changes in the characteristic peaks of the drug in the IR spectra of a mixture of the drug and excipients as compared to IR spectra of pure drug.

The IR spectrum of Tapentadol HCl in pure form exhibits a peak at 3355.99/cm is due to the N-H stretching in tertiary amino group, and peaks at 1642.18/cm are due to C=C aromatic ring, and 1457.97/cm is due to the C-O stretching between phenolic C and O group, thus, confirms the structure of drug. IR studies have shown no interaction between drug and excipients.

It was further confirmed with the differential scanning calorimetry (DSC) studies as shown in Figures 1 and 2. There were no major changes in glass transition temperature of the drug when DSC was performed along with the other excipients. This has been shown in Table 2.

Pre-compression characterization

Core tablet blend

The flow properties of the optimized core formulation blend are shown in Table 3. The results obtained for the angle of repose (θ) were 26.565° which fall within the official range for good flow, i.e., <300. Therefore, the blend has good flow property. The bulk and tapped densities of core tablet blend were 1.69 g/cc and 1.40 g/cc, respectively. Carr's index calculated was found to be 16.56% indicating that the blend has a good flow property. Whereas, Hausner's ratio analyzed was 1.20 representing a good flow.

Press coating material blend

The flow properties of the different outer coating material formulation are shown in Table 4. The results for angle of repose (θ) obtained were found to vary from 22.44 to 36.03 which indicates all the coating material having fairly good flow property and can be used for press coating. The bulk density of outer coating material blend comprised hydroxylpropyl cellulose was found to vary from 0.564 to 0.709 with an increase in its concentration. Carr's index

calculated showed to vary from 12.98% to 19.71% indicating that all the blends have excellent flow property. Whereas, Hausner's ratio analyzed is in 1.15–1.19 range representing a good flow for all the formulation coat powder blends.

Post-compression characterization of core tablets

All the evaluated parameters performed for core tablets are shown in Table 5. The hardness of core tablets was nearly 2.5 kg/cm^2, therefore ensuring appropriate strength. The thickness observed was 3 mm and is even for all tablets. All the (80 mg) tablets selected from the passed uniformity of weight test prescribed in IP. The individual weight of different batch tablets was within the official limits (±10%) of percentage deviation from the average weight. The disintegration time of core tablet was nearly 8 ± 0.002 min. The percentage drug content of all the core tablets 97.05% ± 1.028%, which was also within the acceptable limits.

Table 2: DSC studies comparing drug in pure state and in the formulation

DSC for	Maximum °C	Peak area (J/g)
Pure drug	205.30	145.5
Drug in formulation	202.47	51.22

DSC: Differential scanning calorimetry

Post-compression characterization of press-coated tablets

All the evaluated parameters result obtained from different formulations of press-coated tablets is shown in Table 6. Hardness of various press-coated tablets were in range of 6.2 ± 0.0–7.4 ± 0.22 kg/cm^2. The thickness observed

Table 3: Pre-compression study results for core tablet blend

Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
1.69 g/cc	1.40 g/cc	26.565°	16.56%	1.20

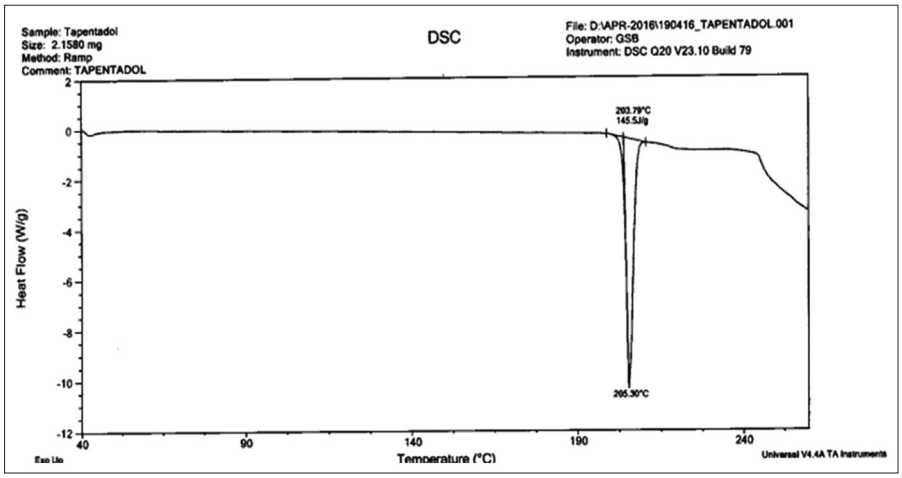

Figure 1: Differential scanning calorimetry thermogram of the drug in pure form

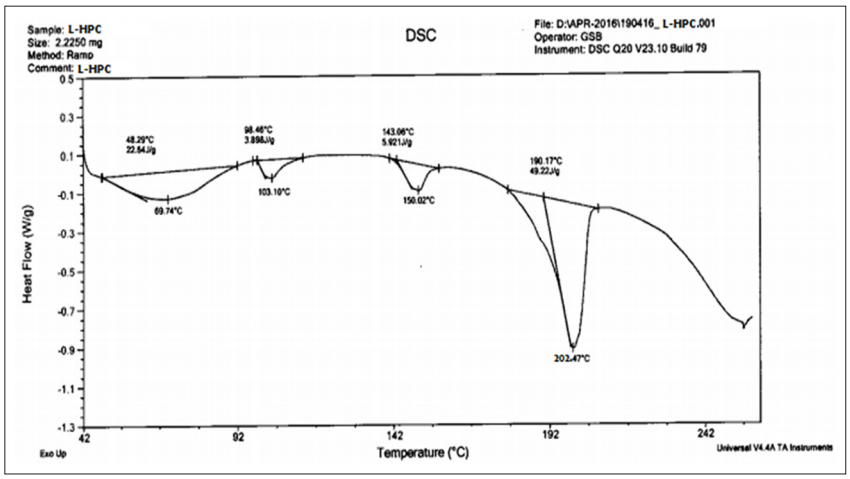

Figure 2: Differential scanning calorimetry thermogram of the drug in the formulation

Table 4: Pre-compression study results for coat powder blend

Formulations	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (°)	Carr's index (%)	Hausner's ratio
F1	0.705+0.03	0.818+0.04	33.60	14.0	1.16
F2	0.63+0.03	0.74+0.07	24.54	17.46	1.17
F3	0.564+0.01	0.650+0.03	26.98	16.07	1.16
F4	0.716+0.02	0.845+0.04	36.03	15.26	1.18
F5	0.710+0.03	0.849+0.03	27.05	19.71	1.19
F6	0.59+0.01	0.68+0.03	22.44	15.25	1.15
F7	0.727+0.01	0.837+0.02	34.33	13.17	1.15
F8	0.735+0.02	0.844+0.06	31.56	12.98	1.15
F9	0.709+0.02	0.832+0.03	31.03	14.78	1.17

Table 5: Post-compression characterization of core tablet

Hardness	Thickness	Avg. weight	Drug content (%)	% Friability	Disintegration (min)
2.5 kg/cm^2	3.5 mm	81±0.005	97.05±1.028	0.56±0.025	8±0.002

Table 6: Post-compression characterization of press-coated tablets

Formulations	Hardness (kg/cm^2)	Thickness (mm)	Avg. Wt. (mg)	Swelling index (%)	Lag time (h)
F1	6.5±0.04	0.5	252	42.54	3.5
F2	6.2±0.05	0.5	251	50.63	2
F3	6.8±0.16	0.5	251	61.92	4.5
F4	6.8±0.12	0.6	296	49.28	4
F5	6.6±0.08	0.7	295	60.52	2.5
F6	7.2±0.25	0.6	298	66.36	4.5
F7	7.0±0.13	0.7	346	52.43	7
F8	6.8±0.55	0.7	342	67.60	3.5
F9	7.4±0.22	0.7	349	27.93	5.5

was from 5 to 7 mm, it was found to be increasing with the weight of coat powder blend. The press-coated tablets selected from different formulation passed the uniformity of weight test prescribed in IP. The individual tablet weights, when compared with average weight, were within the official limit (±5%) of percentage deviation. The friability of all press-coated tablet formulations was within the acceptable limits of 1%. The swelling index was found to vary with the concentration as well as the type of polymers used. Where the main contribution toward swelling of the tablets was the hydroxypropylmethyl cellulose (HPMC) K-100M used.

Dissolution study of core tablets

Based on the results obtained from the dissolution study of core tablets in 0.1N HCl shown in Figure 1 and Table 7, the core tablet formulation provided an extended release of 80% within 7.225 h, zero-order drug release with 0.983 R^2 and 12.68 K value and the mechanism of drug release was found to be Fickian diffusion which was most similar with the Market formulation Nucynta ER 50 and therefore was selected to further formulate the press-coated tablets.

DISSOLUTION STUDY OF PRESS-COATED TABLETS

Tablets were subjected to dissolution in 0.1 N HCl (pH 1.2). The time interval when 10% or more amount of drug was detected in dissolution media was considered as the end of lag time. The dissolution study of these formulations was performed to understand the effect of different polymers and their increasing concentrations. This will inform regarding the suitable polymer among all and its concentration. The optimum formulation was selected based on the criteria of attaining the desired value of lag time and dissolution profile.

The extension in drug release profile was attributed to both the erodible polymer (ethyl cellulose, L-HPC, and Eudragit S-100) and swellable polymer (HPMC K100). With the increase in the weight of the polymers in the formulations,

the drug release profile was found to be affected significantly with increase in the extension time. Formulations F3, F4, and F6 were found to possess optimum lag time of 4–4.5 h as well as drug release profile. F4 was formulated with ethyl cellulose and 50 mg concentration, whereas, F3 and F6 were formulated with L-HPC with 50 mg and 75 mg concentrations, respectively. The lag times were found to be increasing with increase in the weight of the polymer coat material blend in press-coated tablet formulations. However, the effect of Eudragit S-100 in the formulations on lag time was found to be unjustifying.

All formulations prepared with Eudragit S-100 did not show good drug release profile or sufficient lag time thereby can be concluded to be not suitable for press-coated tablets of the chosen drug. The percentage cumulative drug release versus time graphs has been projected in Figures 2-6 to study the effect of the individual polymer.

Table 7: Drug release kinetics of the core tablet

t (80%)	Zero-order		First order		Higuchi	Korsmeyer–Peppas	
	R^2	K	R^2	K	R^2	R^2	N
7.225 h	0.983	12.68	0.858	0.152	0.968	0.983	0.568

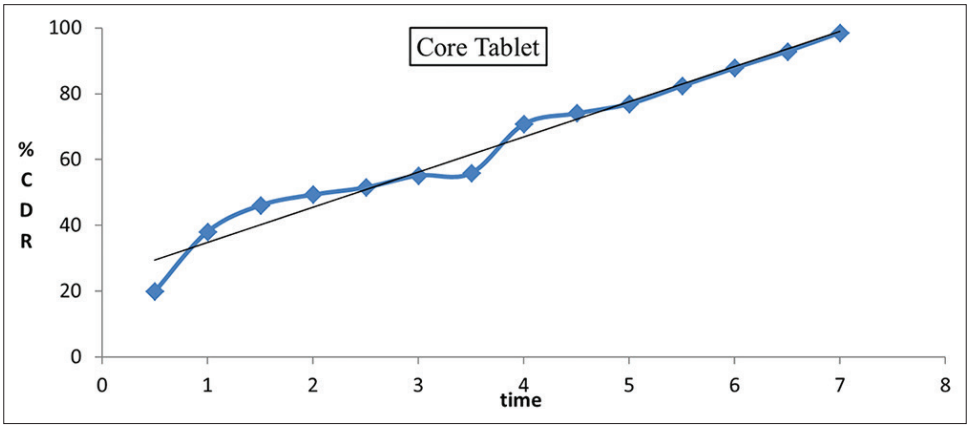

Figure 3: % Cumulative drug release versus time graph for core tablet

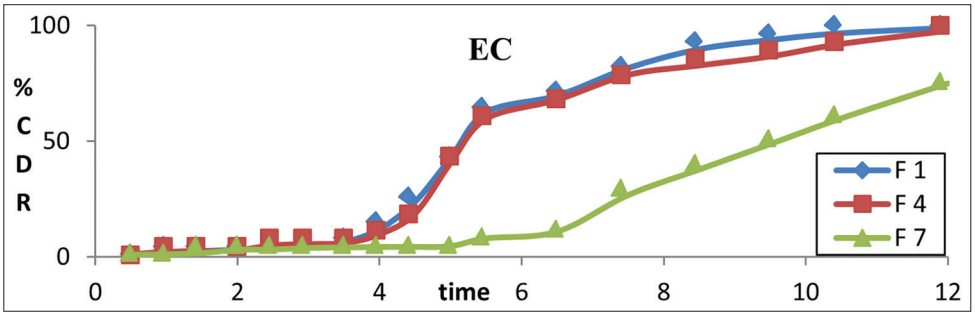

Figure 4: Percentage call detail record versus time graphs for all press-coated tablet formulations with ethyl cellulose

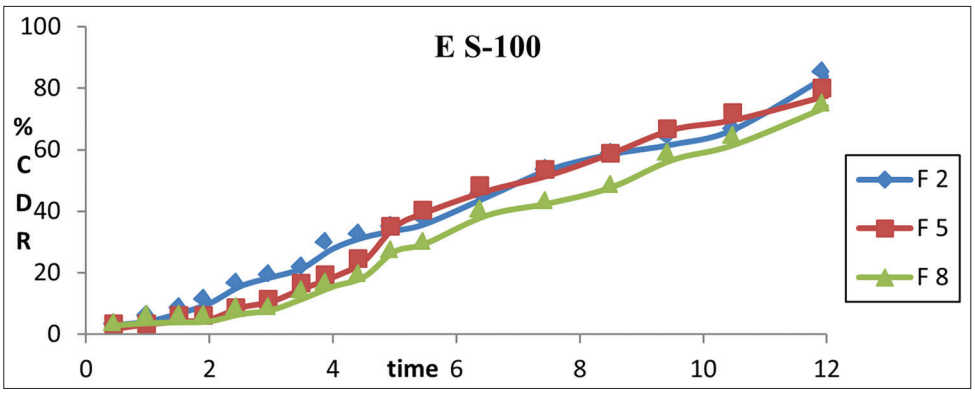

Figure 5: Percentage call detail record versus time graphs for all press-coated tablet formulations with Eudragit S-100

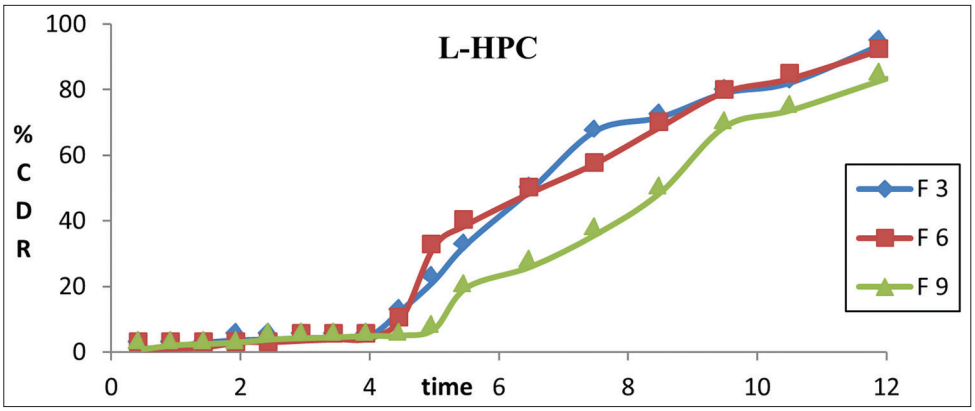

Figure 6: Percentage call detail record versus time graphs for all press-coated tablet formulations with L-hydroxy propyl cellulose

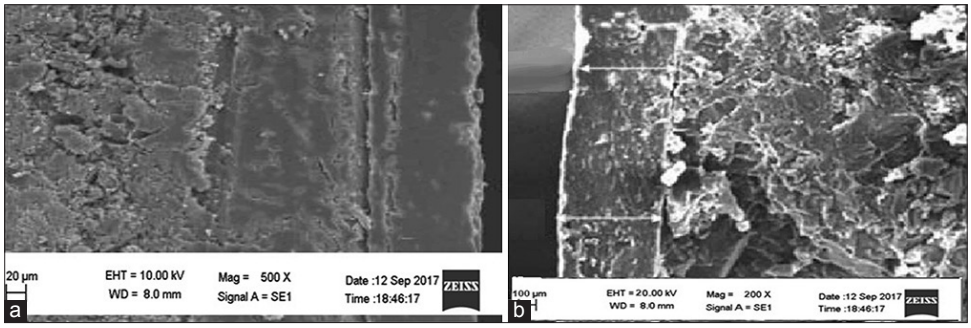

Figure 7: (a and b) Scanning electron microscopy of the selected formulation at 200× and 500× magnification

Scanning electron microscopy

Scanning electron microscopy of the best-selected formulation, containing L-HPC with 50 mg concentration, revealed the distinctive layer of the coating polymer over the core tablet as observed in Figure 7. Uniform coating was observed in all SEM scans. Thereby, ensuring the significant role of the polymer used for press-coating over the core tablet.

CONCLUSION

From the present study, it could be concluded that EC and HPC serve as a potential candidate in the formulating a time-controlled release drug delivery systems with a defined lag time. In comparison to EC, HPC has shown more consistent and predictable lag time. The combinations of EC and HPC can also be studied further to attain reproducible results. The chosen weight ratios of polymers were sufficient to conclude the results. Among all, it can be concluded that formulation with L-HPC of 50 mg concentration was most appropriate to obtain preferred lag time. The amount of HPMC K100 was suitable in maintaining the lag time in the formulations without hindering the results. It helps in increasing the permeability of the press coat, thereby causing pore formation for the drug release after certain lag time.

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