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DEVELOPMENT OF COMPRESSED COATED POLYPILL WITH MUCOADHESIVE CORE COMPRISING OF ATORVASTATIN/CLOPIDOGREL/ASPIRIN USING COMPRESSION COATING TECHNIQUE

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Abstract: The study was conducted to formulate and assess a novel polypill comprising of atorvastatin calcium (ATVC), clopidogrel bisulfate (CLB) and aspirin (ASP) which, after *in vivo* correlation, can be intended for use in hyperlipidemic chronic heart disease patients. Polypill was made by the compression coating technique (CCT) with multiple active ingredients along with different concentrations of mucoadhesive and sustained release polymers, i.e., Carbopol 934 (CAB), Methocel k15 (MTH) and sodium carboxymethyl cellulose (NaCMC). The effect of different concentration of polymers on physical properties, wash off time, mucoadhesion strength, swelling behavior, surface pH and drug release kinetics were investigated. *In vitro* drug release studies showed that combination of CAB-NaCMC (1 : 1) retarded drug release up to 96.7 ± 1.15%, while combination of CAB-MTH and MTH-NaCMC retarded drug release up to 81.9 ± 1.5% and 101.4 ± 1.3%, respectively, at the same polymer concentration. Core enteric coated tablet of ATVC (K11) was compressed over with CLB and ASP granules with the help of CCT and produced the desired results with zero order release rate thus indicating successful formulation of proposed polypill.

Keywords: compression coating technique, kinetics, mucoadhesive, polypill, polymers

Polypill is a fixed dose combination (FDC) which contains three or more medicines in a single tablet with the purpose of minimizing the numbers of dosage forms to be taken by the patient. A polypill concept for minimizing the cardiovascular disease (CVD) risks was first proposed by Wald and Law (1) and has also been applied to other pharmaceutical preparations (2). A polypill containing three generic components could be an attractive approach for patients already taking these medicines separately (3). The polypill may have several advantages including improved delivery of care, increased adherence and reduced cost (4).

Atorvastatin calcium (ATVC) is an antihyperlipidemic agent which is extensively used in patients suffering from CVD to prevent atherosclerosis and related complications. Similar purpose is served by aspirin (ASP) and clopidogrel bisulfate (CLB) through anti-platelet mechanism and both drugs are commonly prescribed to chronic heart disease patients, either alone or in combination (5).

ATVC, CLB and ASP are commonly prescribed drugs in patients suffering from coronary heart disease (CHD) and pose problems of frequent dosing (leading to decreased adherence to prescribed regimen) and drug-drug interactions. These *in vivo* interactions could be reduced by delivering these drugs chronotherapeutically at their respective site. Several approaches are present to develop dosage form with chronotherapeutic delivery and among these approaches simplest approach is to formulate compression coated tablets system (6).

Several issues regarding pharmaceutical formulation were to be addressed before advocating polypill. Polypill formulation comprising of multiple active components is complex and depicts issues regarding bioavailability, pharmacokinetics, drug interactions and drug effects on risk basis that need to be documented (as done with the current polypill preparation) (4).

Compression coating (dry coating or press coating) was one of the first solvent-free coating

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techniques. In this technique the inner core is completely enclosed by the outer layer. The material used in the outer layer controls and aids greatly to the tablet performance including mechanical strength of coated material, drug release pattern and drug stability. In these days and age, pharmaceutical advantages of compression-coated tablets in dosage form development is to protect hygroscopic, light-sensitive, oxygen labile or acid-labile drugs and to separate incompatible drugs from each other to achieve sustained release or modified drug release pattern. Moreover, the compressed core comprising of a sustained release tablet could be coated over by compression with the fast disintegrating formulation. Drug could be present in both core and the outer layer of compressed coated system (7).

To control the mucoadhesion and release of drug (i.e., in the prolonged release component of biphasic system) different polymers could be used to cause mucoadhesion and sustained release of drug from the core tablet. In matrix drug delivery systems, the release mechanism of the drug is fully dependent on the characteristics of the matrix-forming agent. Hydrophilic polymers, due to their ability of swelling up and jellifying when in contact with water, are the most commonly used polymers among all other polymers. A viscous layer is formed due to the gel formation which acts as a protective barrier to both the invasion of water and the efflux of the drug in solution (8).

The present study was aimed to develop compressed coated tablet comprising of sustained release mucoadhesive core for ATVC with Carbopol 934 (CAB) as mucoadhesive polymer and Methocel K15 (MTH) and sodium carboxymethyl cellulose (NaCMC) as the rate controlling polymers by direct-compression technique. The compressed coated layer over core tablet consisted of enteric coated ASP granules and CLB.

EXPERIMENTAL

Materials

Atorvastatin calcium (Morepen Lab Ltd., India), Clopidogrel bisulfate (India Swift Lab, India), enteric coated aspirin (ASP) granules (Vasion Pharmaceuticals, Pakistan), Carbopol 1934 (India Swift Lab, India), sodium carboxymethyl cellulose and Methocel K15 (Zhongbao Chemicals, China), spray dried lactose (FDA Foremost, USA), Talcum (Luna Chem, Taiwan), Avicel PH 102 (Mingtai Chemical. Co. Ltd., Taiwan), stearic acid (Neon Chemicals, Pakistan), mannitol (Quindao Bright Moon Seaweed Group, China), starch (Rafhan, Faisalabad, Pakistan), sodium lauryl sulfate (Sibcon, Karachi, Pakistan).

Preparation of polypill

Preparation of mucoadhesive core tablet of ATVC

ATVC was used in the preparation of core tablets of the compressed coated tablet system at a dose level of 20 mg. The composition of ATVC core tablet is shown in Table 1. Various formulations were prepared using CAB as mucoadhesive polymer and NaCMC and MTH as sustained release polymers with spray dried lactose as filler and talc as lubricant. The powders were sieved through a screen, US-standard mesh # 30 (600 mm), added to sigma mixer (Happy & Marry Business Ltd., China), and mixed for 30 min. The powder blend

Table 1. Formulation of mucoadhesive sustained release ATVC core tablets.

Formulation	ATVC (mg)*	CAB (mg)	SCMC (mg)	MTH (mg)	Spray dried lactose (mg)	Talc (mg)	Core tablet (mg)
K1	22	0	0	0	146	4	172
K2	22	34.5	34.5	0	77	4	172
K3	22	53	53	0	40	4	172
K4	22	60.5	60.5	0	25	4	172
K5	22	34.5	0	34.5	77	4	172
K6	22	53	0	53	40	4	172
K7	22	60.5	0	60.5	25	4	172
K8	22	0	34.5	34.5	77	4	172
K9	22	0	53	53	40	4	172
K10	22	0	60.5	60.5	25	4	172

*22 mg ATVC equivalent to 20 mg atorvastatin calcium (ATCV).

Table 2. Formulation of outer coat layer of compressed coated tablet.

Ingredients	Quantities per compress coated tablet (mg)
Clopidogrel bisulfate (CLB)	104.0
Enteric coated aspirin (ASP) granules	118.3
Avicel PH 102	308.0
Spray dried lactose	104.8
Stearic acid	3.0
Mannitol	43.8
Aerosil	2.5
Starch	10.0
Sodium lauryl sulfate	3.0
Talcum powder	2.5
Total weight	*699.9-700 mg

* Weight to be compressed coated over enteric coated core tablet.

was then lubricated for 3 min and core tablets were prepared by direct compression techniques with the average weight per tablet of 172 mg ± 7.5% by tablet compression machine (ZP17 STC China).

Enteric coating of mucoadhesive core tablets

Enteric coating was done over ATVC core tablets using a mixture of Eudragit E-100 in isopropyl alcohol (IPA) and methylene chloride as sealing coat. The process continued for 2 h using a test batch coating pan (STC, China). After sealing coat, enteric coat was applied using a mixture of Eudragit L-100 in IPA and methylene chloride in the ratio of 1 : 10 : 7. The pan speed was set at 18 rpm under the temperature of 60-70^{o}C. The process was done in 4 h and temperature was gradually decreased as the process of enteric coating continued. At the end of the process, the total weight gain by the core tablet was around 8 to 10%.

Compression coating of CLB and enteric coated ASP granules over optimized enteric coated core tablets of ATVC

On the optimized formulation of core tablet, the outer coat of the compressed coated tablet was prepared using CLB and prefabricated enteric coated ASP granules. Avicel PH 102 was added as tablet disintegrant, spray dried lactose as filler, stearic acid as lubricant, mannitol as sweetening agent, aerosil as glident along with sodium lauryl sulfate and talc (Table 2). All the ingredients were sieved and mixed together in a cone mixer (Happy & Marry Business Ltd., China) for 30 min. After the stated time, the mixture was transferred to the compression coating machine (ZP33 STH China, modified). The machine operates in such a way that the core tablet was compressed in between the coated powder mixture. The weight of the outer coat layer was around 700 mg ± 5% per tablet and total weight of the compressed coated tablet system was 900 mg ± 5% per tablet.

Physical characterization of core tablets and compressed coated tablets

Physical tests

The core tablets and compressed coated tablets were characterized for weight variation (electrical weighing balance JK 180, Chyo), thickness and diameter (vernier caliper SH.0281, China), hardness (automatic hardness tester, Curio) and friability (Roche friabilitor).

Ex vivo mucoadhesive strength of core tablets

The core tablets were evaluated for their mucoadhesive strength using a modified physical balance method. A fresh rabbit intestine was obtained and used within 2 h of dissection. The intestine was cut into pieces, washed with distilled water and phosphate buffer pH 7.3 at 37 ± 0.5^{o}C. The pieces of intestine were fitted over the mouth of glass vials. One vial was hanged upside down using threads and hanging clips on the left side of the physical balance. The second vial was made to stick tightly in the center of the glass beaker containing phosphate buffer (pH 7.3 at temperature 37 ± 0.5^{o}C). The core tablet was placed between the intestine fitted mouths of glass vials and allowed to adhere for 5 min. Water (equivalent to weight) was added slowly at 100 drops/min into a small beaker placed in the right hand pan until the tablet detached from the intestinal surface (9). The weight at which

the two vials detach from each other was noted. For each formulation triplicate readings were taken and the following formula was used for the calculation of mucoadhesive force using mucoadhesion strength.

$$Force\ of\ adhesion = \frac{Mucoadhesion\ strength}{1000} \times 9.81$$

Ex vivo mucoadhesion time (wash off test) of core tablet

The *ex vivo* mucoadhesion time was evaluated (n = 3) using *in vitro* wash off methods. The wash off tests was conducted by two separate methods, i.e., disintegration apparatus method and dissolution apparatus method.

Wash off test using disintegration apparatus method

Pieces of rabbit intestinal were tied to the outer side of the basket of disintegration apparatus and core tablets were attached over it. The basket was then assembled in the disintegration apparatus (121-L Galvano Scientific, Pakistan) and filled with phosphate buffer pH 7.3 at 37 ± 0.5°C. Time of detachment of tablet from intestine for each formulation was noted (10).

Wash off test using dissolution apparatus method

A glass slide covered with pieces of inverted rabbit intestine was attached to the paddle arm of the USP paddle apparatus (GDT-6L Galvano Scientific, Pakistan). The core tablets were attached on intestine covered glass slides. The paddle arms were dipped in phosphate buffer pH 7.3 at 37 ± 0.5°C. The dissolution apparatus was operated at 50 rpm and tablet detachment time from the intestine was noted (11).

Swelling index test of core tablet

Core tablets were placed separately in a beaker containing 50 mL of phosphate buffer at pH 7.3 at 37°C. Readings were taken after an interval of 1 h up to 24 h time period. Triplicate readings were taken for each formulation. Swelling index was calculated by the following equation (12):

$$Swelling\ index\ (S.I.) = \frac{W_2 - W_1}{W_1} \times 100$$

where, W_2 = weight of tablet at time t; W_1 = weight of tablet before placing in the beaker.

Surface pH test of core tablet

The core tablets were placed in a small beaker with 10 mL of distilled water and allowed to swell for 2 h. Afterwards, the glass electrode of pH meter was brought closer to the surface of core tablet and surface pH was noted after equilibrating for 1 min (n = 3) (10).

Enteric coating disintegration test

Enteric coated tablets (n = 6) were placed in a basket rack assembly of USP disintegration apparatus containing simulated gastric fluid (SGF) maintained at 37 ± 0.5°C. After 2 h, SGF was replaced with phosphate buffer pH 7.3, maintained at 37± 0.5°C and operated for 30 min.

Disintegration testing of compressed coated tablets

Compressed coated tablets (n = 6) were randomly selected and placed in a basket rack assembly of disintegration apparatus containing SGF at 37 ± 0.5°C.

***In vitro* dissolution studies**

In vitro drug release testing (core tablets)

For core tablet containing ATVC, *in vitro* drug release studies were performed using USP dissolution paddle apparatus containing 900 mL of phosphate buffer pH 7.3, maintained at 37 ± 0.5°C, with rotation speed of 100 rpm. Samples of 10 mL were withdrawn from the dissolution apparatus after 1 h over a period of 12 h, filtered and spectrophotometrically quantified through a UV/Visible spectrophotometer at 244 nm. The cumulative fraction of the drug released was calculated from the total amount of atorvastatin calcium and plotted as a function of time (13).

***In vitro* drug release testing of compressed coated tablets**

The *in vitro* drug release studies were performed on the compressed coated tablets using Dissolution Apparatus I-Rotating Basket (GDT-6L Galvano Scientific, Pakistan) containing 900 mL of HCl buffer (pH 2) maintained at 37 ± 0.5°C at 50 rpm for 30 min. Sample of 10 mL, containing dissolved CLB, was withdrawn after 30 min, filtered and quantified under UV/Visible spectrophotometer (1700 Shimadzu, Japan) at 240 nm. Subsequently, the baskets were removed from the dissolution apparatus containing undissolved enteric coated ATVC core tablets and enteric coated ASP granules. ASP enteric coated granules were collected from each basket, washed and transferred to USP dissolution apparatus I-Rotating basket containing phosphate buffer pH 6.8 maintained at 37 ± 0.5°C and operated at 100 rpm. A sample of 10 mL was removed after 90 min and studied for ASP contents spectrophotometrically at 265 nm.

Drug release data modeling

The suitability of several equations that are reported in the literature to identify the mechanisms for the release of atorvastatin calcium was tested with respect to the release data. Therefore, three kinetics models including the zero-order release equation, Higuchi equation and first-order equation were applied to analyze the *in vitro* data to find the equation with best fit (14).

Zero-order model: $Q = k_1 t$

Higuchi model: $Q = k_2 t^{1/2}$

First-order model: $Q = 100e^{kat}$

where "Q" is the percentage release of drug at time t; k_1, k_2 and k_3 are the rate constants for zero-order, Higuchi and first order model, respectively.

Statistical data analysis

For statistical data interpreatation, MiniTab® 17.1.0 software was used. Analysis of variance (ANOVA) with $p < 0.05$ as a minimal level of significance was used to interpret statistical difference between *in vitro* dissolution. A 3-D surface plot at 10th hour was constructed to analyze the effect of polymer concentration of the release rate of ATVC from matrix tablet (13).

RESULTS

All the core tablets formulations showed acceptable properties and complied with the in-house specifications for friability, weight variation, diameter and hardness (Tables 3 and 4).

Ex vivo mucoadhesive strength was determined for all formulations, using rabbit intestine (Table 4). Core tablets K4, containing CAB and NaCMC (1 : 1), showed higher values of mucoadhesion strength i.e. 0.477 ± 0.009 N. The mucoadhesion time on rabbit intestine for all formulations ranges from 0 to 752 ± 1.53 min and 10 ± 1.53 to 805 ± 4.04 min for disintegration apparatus method and dissolution apparatus method, respectively. Core tablets containing CAB and MTH (1 : 1) showed higher values of mucoadhesion time.

The swelling index test was conducted on all formulations and the highest swelling index was found in formulation K10 containing 70% MTH and NaCMC (1 : 1) after 20 h (Table 5). The degree of swelling of bio-adhesive polymers is an important factor affecting adhesion to the biological membrane (15).

The values of surface pH are given in Table 5. Mucosal irritation can be caused by an acidic or alkaline formulation and hence, surface pH is an important parameter in developing a mucoadhesive dosage form (10).

The patterns of *in vitro* drug release studies (Table 6) showed gradual increase in sustain release effects for formulation K2 to K4 containing CAB and NaCMC (Fig. 1). A complete drug release was achieved in K2 and K3 after 12 h ($p < 0.01$).

Table 3. Physical tests performed on mucoadhesive sustained release ATVC core tablet.

Formulation	Friability (%)	Weight variation (mg)	Hardness (kg/cm^2)	Diameter (mm)	Thickness (mm)
K1	0.50 ± 0.03	172.7 ± 0.83	8.9 ± 0.10	7.99 ± 0.02	3.62 ± 0.04
K2	0.60 ± 0.02	177 ± 0.76	7.5 ± 0.30	8.03 ± 0.02	3.49 ± 0.02
K3	0.66 ± 0.07	168 ± 0.76	9 ± 0.15	7.93 ± 0.04	3.58 ± 0.03
K4	0.68 ± 0.07	173.7 ± 0.42	8.8 ± 0.51	8.01 ± 0.02	3.59 ± 0.03
K5	0.53 ± 0.05	180.5 ± 0.40	11.1 ± 0.35	8.01 ± 0.03	3.51 ± 0.02
K6	0.56 ± 0.03	170.6 ± 0.85	10.8 ± 0.55	8.02 ± 0.03	3.81 ± 0.02
K7	0.60 ± 0.06	177.9 ± 0.87	10.5 ± 0.50	8.01 ± 0.03	3.53 ± 0.06
K8	0.58 ± 0.05	173.2 ± 0.81	10.7 ± 0.76	7.98 ± 0.04	3.43 ± 0.06
K9	0.60 ± 0.07	178.8 ± 0.35	10.8 ± 0.35	7.99 ± 0.03	3.43 ± 0.05
K10	0.59 ± 0.04	176.4 ± 0.82	10.2 ± 0.56	8.01 ± 0.04	3.56 ± 0.01

Triplicate readings (n = 3).

Table 4. Results of physical tests performed on compressed coated tablets.

Compressed coated tablet	Weight variation (mg)	Hardness (kg/cm^2)	Diameter (mm)	Thickness (mm)	Disintegration time (s)
	901.5 ± 8.71	4.43 ± 0.31	12.91 ± 0.05	7.02 ± 0.07	45.3 ± 3.08

Formulations K5, K6 and K7 with MTH and CAB had relatively good sustained release actions (Fig. 2). The complete drug release was seen in formulation K5 but for formulations K6 and K7 the drug release was 86.5 ± 1.58% and 81.8 ± 1.50%, respectively, after 12 h of study ($p < 0.01$). Formulations K8, K9 and K10, consisting of NaCMC and MTH (1 : 1), showed complete drug release within 8, 9 and 11 h, respectively ($p < 0.01$) (Fig. 3). The formulations better fitted in zero kinetic model, except for K8 which seemed to follow Higuchi model because of better R^2 value (Table 7). The 3D-surface plot at t_{10} (Fig. 4) signified that the increase in polymer concentration (as a combination in the same ratio) increased the drug release from mucoadhesive core tablet.

Formulation K5 was selected as an optimized formulation based on *ex vivo* mucoadhesion strength (0.26 ± 0.008 N at 5 min contact time), mucoadhesion time (665 min ± 1.53 and 728 min ± 3.79), swelling index (1202.8 ± 1.61%), surface pH (5.57 ± 0.02) and *in vitro* drug release (100 ± 1.5% in 12 h following zero order release pattern).

Formulation K5 was subjected to enteric coating for its most sustained *in vitro* dissolution profile, formulation was found to be intact after 2 h testing in SGF and dissolved within 30 min in phosphate buffer pH 7.3.

Compressed coated tablet system escorting core tablet K5 showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, hardness, diameter

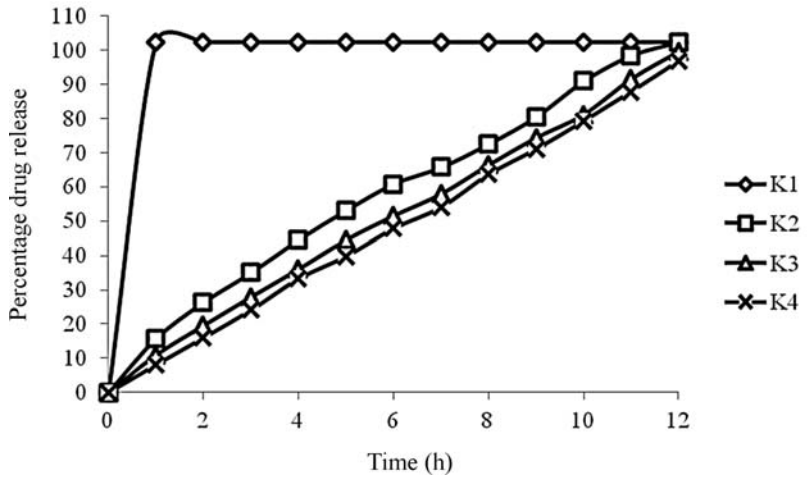

Figure 1. *In vitro* drug release study of core tablet of ATVC containing mucoadhesive polymer (n = 3)

Table 5. Mucoadhesion force, washout time, swelling and surface pH of core tablet of ATVC.

Formulation	Mucoadhesive force (N)	Washout time in disintegration apparatus (min)	Washout time in dissolution apparatus (min)	Swelling	Surface pH
K1	0.000	0 ± 0.00	10 ± 1.53	0.0 ± 0.00	5.45 ± 0.04
K2	0.148 ± 0.006	660 ± 4.04	681 ± 1.53	1363.9 ± 2.70	6.13 ± 0.01
K3	0.208 ± 0.003	752 ± 1.53	770 ± 2.08	1466.5 ± 1.19	6.19 ± 0.02
K4	0.398 ± 0.004	635 ± 2.52	745 ± 2.08	1473.3 ± 1.80	6.24 ± 0.03
K5	0.260 ± 0.008	665 ± 1.53	728 ± 3.79	1202.8 ± 1.61	5.57 ± 0.02
K6	0.288 ± 0.007	728 ± 4.00	781 ± 2.08	1316.5 ± 2.90	5.25 ± 0.03
K7	0.301 ± 0.005	751 ± 2.65	805 ± 4.04	1436.5 ± 2.37	5.05 ± 0.02
K8	0.168 ± 0.003	558 ± 1.53	652 ± 3.79	1396.0 ± 1.52	6.89 ± 0.03
K9	0.229 ± 0.010	684 ± 2.52	745 ± 1.53	1532.74 ± 1.18	6.7 ± 0.04
K10	0.232 ± 0.002	705 ± 3.21	784 ± 2.65	1803.39 ± 2.65	6.66 ± 0.04

Table 6. *In vitro* dissolution study of core tablet of ATVC.

Time	K1	K2	K3	K4	K5	K6	K7	K8	K9	K10
0	0.00	0.00	0.00	0.00	0	0.00	0.00	0.00	0.00	0.00
1	102.34	15.74	10.98	8.14	10.857	8.34	6.43	20.19	14.59	14.44
2	102.34	26.35	19.62	16.01	20.45	16.00	12.54	36.05	28.67	26.00
3	102.34	35.02	27.97	24.10	28.423	22.77	17.55	50.86	42.93	38.17
4	102.34	44.54	36.11	33.25	36.34	28.33	22.46	64.43	57.71	50.32
5	102.34	53.08	44.57	39.76	43.347	34.45	27.40	78.33	69.92	61.55
6	102.34	60.80	51.56	47.80	51.617	43.61	33.70	90.23	78.94	71.33
7	102.34	65.71	57.95	53.98	60.403	50.66	40.79	98.12	87.37	79.72
8	102.34	72.50	66.43	63.58	71.973	58.10	48.36	101.34	96.26	86.55
9	102.34	80.43	74.40	70.95	81.433	67.45	56.37	101.34	102.08	94.56
10	102.34	90.91	81.17	79.18	88.327	73.68	64.56	101.34	102.09	97.88
11	102.34	98.38	91.58	87.77	94.607	79.63	71.66	101.34	102.09	101.36
12	102.34	102.38	99.65	96.72	100.15	86.56	81.86	101.34	102.09	101.36

Table 7. Values of release constant 'k' and regression coefficient 'R^2' obtained from data of ATCV core tablet.

Formulation	Zero order		First order		Higuchi	
	R^2	$k_{1\,(\%h^{-1})}$	R^2	$k_{2\,(\%h^{-1})}$	R^2	$k_{3\,(\%h^{-1})}$
K1	0.2143	3.3375	0.2143	0.1522	0.4498	18.682
K2	0.9879	8.0709	0.6254	0.2504	0.9582	30.711
K3	0.9969	7.9371	0.6684	0.2647	0.9388	29.759
K4	0.9990	7.9183	0.7337	0.2771	0.9195	29.351
K5	0.9900	6.6028	0.7001	0.2706	0.9309	31.611
K6	0.9986	7.2302	0.7403	0.2716	0.9186	26.793
K7	0.9969	8.4666	0.7924	0.2774	0.8787	24.034
K8	0.8486	8.3620	0.5208	0.2380	0.9186	26.793
K9	0.9140	8.9293	0.5864	0.2556	0.8787	24.034
K10	0.9562	8.7222	0.6142	0.2572	0.9465	34.121

and thickness. The disintegration test for the compressed coated tablet comprising K5 core formulation was performed using USP tablet disintegration apparatus (Table 4).

The *in vitro* drug release study on compressed coated tablets was conducted for 2 h in which 30 min testing was conducted in HCl buffer medium (pH 2) for CLB. Subsequently, enteric coated granules of ASP were collected and tested in a buffer of 6.8 pH. The CLB release was found to be 100.9 ± 0.85% after 30 min whereas ASP results were recorded to be 101 ± 0.90% after stated time.

DISCUSSION

This study aimed to formulate an optimized polypill formulation which would provide an optimal *in vitro* drug release pattern and later be correlated with physiological pattern in high risk patient. The *in vivo* release pattern desired are associated with fewer heart attacks, blockage of the arteries, greater improvements in total 'good' cholesterol and better blood vessel function. Moreover, such release pattern may reduce drug-drug interactions and increased compliance (16).

CAB and MTH were selected as mucoadhesive polymers because they are reported to be good mucoadhesives for polypill formation (17). NaCMC has been shown to retard the drug release because of its swelling properties in aqueous media (18). Various formulations were made using these polymers at different concentrations and optimized during preliminary trials to find the best formulation for compressed coated system with mucoadhesive core

system. All the tests were performed in HVAC system due to the tendency of these polymers to absorb moisture from the environment.

Mucoadhesive core tablets were found to be satisfactory when evaluated for weight variation, thickness, hardness, and friability. Table 3 shows that as the polymer concentration increased, the friability of core tablets also increased due to an increase in moisture absorbing affinity of polymers. Multi-ingredient tablets formulated with similar methodology have been satisfactory in fulfilling pharmaceutical standards in previous studies (19).

Mucoadhesive strength proportionally increased with increase in polymer concentration in all formulations as demonstrated by previous studies (20, 21). The results showed that K4 containing CAB and NaCMC (1 : 1) was the best polymer combination with respect to mucoadhesion strength. As CAB and MTH both are mucoadhesive polymers, mucoadhesion time or washout time in dissolution apparatus suggested that the best polymer combination concerning mucoadhesion was K7 which was greater than any other polymer combinations i.e., CAB and NaCMC and MTH and NaCMC. A decrease in washout time observed with an increase in NaCMC concentration (K4) was due to the fact that NaCMC is a swellable polymer rather than a mucoadhesive polymer (22). Therefore, as the time increased, the tablet became heavier and detached earlier from rabbit's intestine.

From the results it was observed that the increase in polymer concentration was directly proportional to the swelling of the core tablets. The hydration ability of a formulation is important

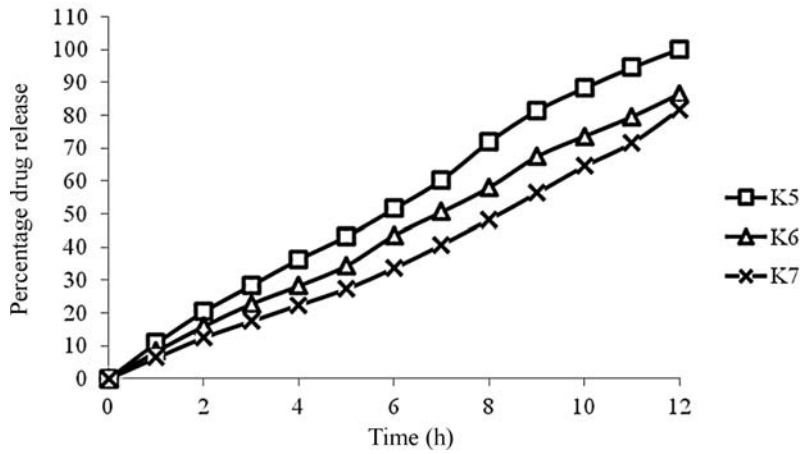

Figure 2. *In vitro* drug release study of core tablet of ATVC containing mucoadhesive polymer (n = 3)

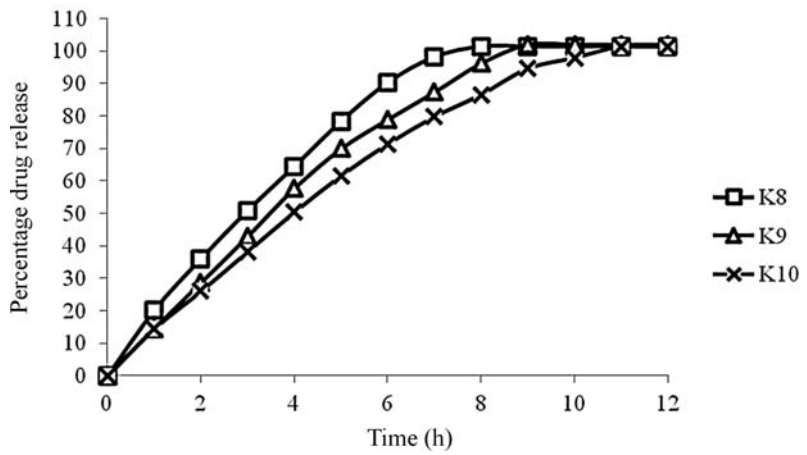

Figure 3. *In vitro* drug release study of core tablet of ATVC containing mucoadhesive polymer (n = 3)

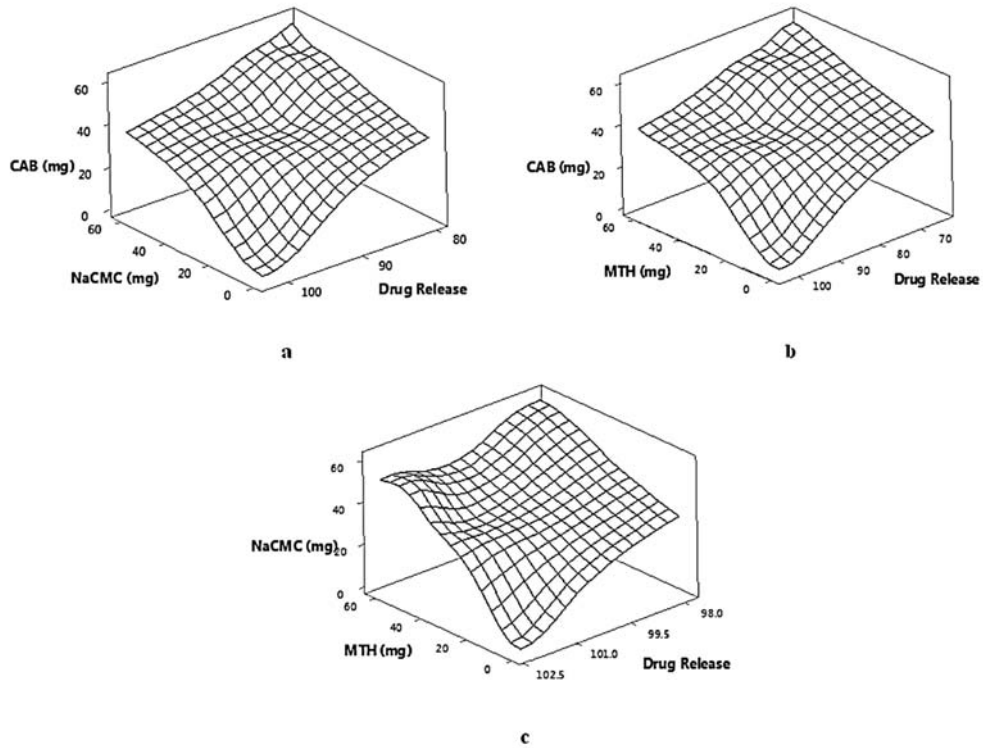

Figure 4. 3D-surface plot at t_{10} of core tablet of ATVC (a: CAB : NaCMC; b: CAB : MTH; c: (NaCMC : MTH)

because it influences tablet buoyancy, adhesion ability of swellable polymers and drug release kinetics (23). The water absorbing capacity of the test formulation depends on type and ratio of polymers. The highest swelling was seen in K10 with polymer combination of MTH and NaCMC at highest polymer concentration due to increased tendency of NaCMC to absorb water and swell (24), and the lowest swelling index values were obtained with polymer combination of CAB and MTH because CAB has lesser tendency to absorb water and swell as compared to NaCMC. These findings correlate with optimal release pattern desired (25). The surface pH test was conducted on core tablets to investigate the *in vivo* side effects, as acidic or alkaline formulation can cause severe irritation to the intestinal mucosa. The surface pH test suggested that K7 (CAB and MTH) was the most suitable polymer combination regarding surface pH. This is because both are acidic polymers. On the other hand, formulations containing NaCMC had a more basic proximity because of the basic nature of NaCMC as compared to CAB and MTH (26).

As K1 had no sustained release polymer, therefore an immediate drug release was observed. Sustained release pattern was observed in formulations as the polymer concentration was increased. Increased concentration of CAB decreased the *in vitro* release of drug. Increasing NaCMC concentration also has the similar effects as increasing CAB (27). Formulations K5, K6 and K7 (MTH and CAB) had best sustained release patterns among all other formulation groups. A high percentage of carboxylic acid groups in CAB are responsible for swelling property of the polymer. In addition to the hydrophilic nature of CAB, its cross-linked structure and water insolubility makes CAB a potential candidate for use in controlled drug delivery system (CDDS) (28). MTH is used as a gel forming polymer in the formulation of CDDS. The diffusion of drug through this gel barrier is controlled by the degree of hydration which, in turn, is dependent on the polymer concentration, the viscosity grade and excipients (29). The least sustained effect was observed in formulation K8, K9 and K10 containing MTH and NaCMC. The rapid dissolution of the

tablet was characterized to the presence of carboxylic group in NaCMC. Although MTH and NaCMC have synergistic effect in increasing the viscosity when used in combination, but this did not lead to an increased resistance to erosion. In the dry state, the drug is homogenously distributed in the polymer matrix system. On hydration of the surface of the tablet a gelatinous layer is formed which upon further hydration causes an osmotic pressure from within the structure of the hydrogel that causes the release of drug; without polymer itself getting dissolved. This gel layer around the tablet core acts as a rate controlling membrane, which results in linear release of the drug (28). At lower polymer concentration and increased spray dried lactose concentration, the rate of drug release increased because of an increase in porosity caused by the dissolution of lactose. Spray dried lactose has high water solubility which facilitates water penetration into the matrix tablet, which subsequently causes disintegration and rapid release of drug from the matrix system.

Formulations K1 did not fit in any of the kinetic models because the regression coefficient (R^2) values were found to be less significant due to lesser polymer concentration and no controlled or sustained release effect. Formulation K8 was better fitted in Higuchi model which shows that there was negligible chances of drug matrix swelling and drug diffusivity was constant, while formulations K2, K3, K4, K5, K6, K7, K9 and K10 were best fitted in zero order kinetics which shows that the dosage form did not disaggregate and drug release was slow and constant (30).

CONCLUSION

The polypill formulation can be carried out successfully with three proposed drugs using suitable concentration of NaCMC and CAB for producing an optimum dosage form which would comply with standard parameters of delayed release (ATVS and ASP) and standard release (CLB) dosage forms. The formulation K5, as core tablet, was selected for the compressed enteric coating because of the desired mucoadhesion strength, mucoadhesion time, surface pH and *in vitro* dissolution studies. The formulation provided desired *in vitro* sustained release pattern with zero order drug release kinetics and might lead to beneficial pharmacokinetics profile as a core tablet for compressed coated polypill. Compressed coated tablet system (polypill) complied with the in-house specifications for weight variation, hardness, diameter and thickness with acceptable immediate and sustained release characteristics.

Conflict of interest

The authors declare no conflict of interest.

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