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DEVELOPMENT AND EVALUATION OF FLAVOXATE HCl DOUBLE CORE COMPRESSED TABLET FORMULATIONS BY SWELLABLE GRANULATION TECHNIQUE

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Abstract: The objective of the proposed research was to develop double core differential release tablets of Flavoxate HCl, a smooth-muscle relaxant through the swellable technique. Inner core granules were prepared by a wet granulation method using HPMC K15 and Kollidon as sustained-release polymers. Outer core immediate release granules were also prepared by a wet granulation method using standard tableting excipients. Both types of granules were evaluated for pharmaceutical, structural, and thermal parameters. The double core tablet was prepared using a pre-compressed inner tablet. *In vitro* release studies were performed in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4) as dissolution media. Stability studies were also performed on the selected formulations. Pharmaceutical evaluation results of inner core granules prepared by HPMC K15 and Kollidon and tablets showed acceptable values for all the physical parameters. FTIR studies showed that the principal peaks of the drug remained intact, indicating no chemical interaction occurred between drug and a polymer. DSC results showed no noteworthy change in the thermal behavior of the drug while in granular formulation. Inner core tablets were successfully compressed with acceptable results of friability, hardness, thickness, diameter, and content uniformity parameters. Double core tablets were prepared by employing immediate release granules as the outer core with intact tablets as the inner core, and all the uniformity parameters of the prepared tablets were found to be within the acceptable limits. *In vitro* release studies in both media showed a characteristic sustained drug release pattern for up to 24 hours. Results of stability studies indicated that all the formulations remained stable.

Keywords: Flavoxate, swellable, double core, HPMC K15, Kollidon, polymer

Swellable matrices are either homogeneous or heterogeneous monolithic systems that are specifically used for the drugs that require frequent dosing. The polymers employed in these systems usually swell to form hydrogels when in contact with water (1). In swellable granulation, the drug delivery primarily depends on the outer gel layer, formed on the matrix surface because of polymer transition in dissolution media. This technique can also be helpful to prolong the drug delivery from the drug product because of the continuous swelling of polymeric substances. The drug release from the dosage form is mainly dependent on the interaction among the drug, polymer, and water (2, 3).

Hydroxypropyl methylcellulose (HPMC K15) is a biocompatible, swellable hydrophilic polymer,

which is widely used for the controlled delivery of drugs from the dosage form (4). Kollidon SR is a pH-independent sustained release polymer, composed of 80% Polyvinyl acetate and 19% povidone in a physical mixture, stabilized with 0.8% sodium lauryl sulfate and 0.2% colloidal silica. It is insoluble in water and very soluble in N-methylpyrrolidone.

Flavoxate, a smooth-muscle relaxant, works by relaxing the muscles in the bladder. It helps to prevent more frequent micturition and bladder pain. Its normal adult dose is 100–200 mg per oral 3 to 4 times daily. It is normally excreted via kidneys with 10–30% of the dose being excreted in urine within 6 h of dosing and 57% being excreted within 24 h of dosing (5). Its metabolite 3-methyl-flavone-8-carboxylic acid (MFCA) appears in urine both as free and conjugated

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form (6). The absolute bioavailability of the drug is 90%. All these properties make Flavoxate HCl an ideal candidate for the development of a sustained-release formulation to reduce the frequency of dosing. Therefore, the present study was carried out to develop a Flavoxate double core tablet formulation containing an immediate-release layer for attending the fast onset of action and sustained release core using a swellable matrix technique with HPMC K15 and Kollidon SR as polymers and Povidone K30 as a binder (7-9). The swellable matrix formulations have been reported to have many advantages such as reduction in the size of a tablet as compared to hot melt granulation technique, better control over the drug release, and lesser side effects (10). In this study, nine batches each of HPMC K15 and Kollidon SR were prepared separately and evaluated for pharmaceutical properties.

EXPERIMENTAL

Materials

Flavoxate HCl, HPMC K15, Kollidon SR, and Povidone K30 were gifted by Pacific Pharmaceuticals (Lahore, Pakistan). All the other chemicals, i.e., Citric acid, Magnesium stearate, and Aerosil were

obtained from Merck, Germany, while Avicel was obtained from Mingthai, Taiwan.

Manufacturing of double core tablets

Double core tablets containing sustained-release inner core granules and immediate release outer core were manufactured by the following methods.

Preparation of inner core granules

Nine batches of Flavoxate HCl inner core granules were manufactured by using different quantities of HPMC K15 and Kollidon SR as shown in Table 1. The weighed quantity of the binder was mixed with distilled water to make the paste. Weighed quantity of Flavoxate HCl and polymer (HPMC K15 and Kollidon SR) was passed from sieve No. 16 and mixed geometrically. Afterward, the binder paste was gradually added into the mixer and further mixed for ~2 min. The wet mass was dried at $50 \pm 5^\circ\text{C}$ for 3 h and was converted into granules by using an automatic Granulator (Sieve No. 12). The granules were then mixed with magnesium stearate and citric acid for 10 min (11). To evaluate the properties of granules various quality control tests, i.e., sieve analysis, bulk and tapped density, loss on drying (LOD), and content uniformity test were performed according to the standard procedures (12).

Table 1. Composition of Flavoxate HCl sustained release inner core with HPMC K15 and Kollidon SR.

Formulation	HPMC K15	Citric acid	Povidone K30 (mg)	Magnesium stearate (mg)	Kollidon SR (mg)	Kollidon SR for paste (mg)	Wt. of tablet (mg)
ICG _{H-WG} -I	50	10	20	10	-	-	590
ICG _{k-WG} -I	-	-	-	5	50	10	590
ICG _{H-WG} -II	65	10	25	10	-	-	610
ICG _{k-WG} -II	-	-	-	5	55	15	590
ICG _{H-WG} -III	90	10	30	10	-	-	640
ICG _{k-WG} -III	-	-	-	5	45	20	590
ICG _{H-WG} -IV	100	10	30	10	-	-	650
ICG _{k-WG} -IV	-	-	-	5	50	15	590
ICG _{H-WG} -V	100	15	30	10	-	-	655
ICG _{k-WG} -V	-	-	-	5	50	15	590
ICG _{H-WG} -VI	100	20	30	10	-	-	660
ICG _{k-WG} -VI	-	-	-	5	50	10	590
ICG _{H-WG} -VII	100	10	30	10	-	-	650
ICG _{k-WG} -VII	-	-	-	5	50	15	590
ICG _{H-WG} -VIII	100	15	30	10	-	-	655
ICG _{k-WG} -VIII	-	-	-	5	55	20	590
ICG _{H-WG} -XI	100	20	30	10	-	-	660
ICG _{k-WG} -XI	-	-	-	5	55	15	590

*H-WG stands for formulation prepared by wet granulation using HPMC K15& k-WG for formulation prepared by wet granulation using kollidon SR

Preparation of outer core granules

Three different immediate release granule batches of Flavoxate HCl were prepared using the wet granulation approach for the outer core, labeled as OCG_{WG}-I to OCG_{WG}-III (Table 2). Each outer core granules formulation was prepared by blending Flavoxate HCl (100 mg) and Avicel PH 101 as given in Table 2 (13). Both ingredients were sieved and mixed uniformly in a lab-scale mixer (Khan engineering, Lahore, Pakistan). The weighed quantity of Povidone K30 was mixed with 1 L of the distilled water. In order to form a smooth paste, the resultant solution was heated to 60°C to completely dissolve the Povidone K30. The paste was added gradually into the mixer of Flavoxate HCl and Avicel PH 101 and was mixed at slow speed for about 2 min (14). The granules were subjected to various tests, including physical appearance, sieve analysis, density studies, loss on drying, DSC, FTIR analysis, and content uniformity using the validate HPLC method described elsewhere.

Differential calorimetry scanning (DSC)

Differential scanning calorimeter (DSC) was used for thermal analysis of Flavoxate HCl granules for inner as well as outer core. The test was carried out with 5.0 mg of Flavoxate HCl granules. These granules were sealed in a 30 µL aluminum pan and scanned at 10-300°C at a heating rate of 10°C/min (15).

FTIR spectroscopy

Fourier Transform Infrared (FTIR) spectra were recorded for the pure drug, inner core, and outer core granules by using an FTIR spectrophotometer (Alpha-P Bruker, Germany), equipped with an ATR unit across the range of 4000-400 cm⁻¹.

Compression of sustained-release inner core tablets

All the inner core granules formulations prepared by using different polymers (Table 1), were compressed into tablets using a rotary compression machine (Killian RUD, Germany) having 20 stations

capable to make double core tables. It is a specialized machine capable of making double core tablets. The machine is equipped with two different hoppers, one is meant for pre-compressed tablets used as the inner core, whereas the other hopper is meant for the transfer of outer core granules to make a tablet within the tablet (double core tablets). The inner core was compressed using round, convex punches having a diameter of 12 mm. The inner cores tablets were subjected to physical tests, including appearance, diameter, friability, hardness, thickness, and weight variation according to official British Pharmacopeia (BP) methods (12).

Compression of double core tablets

Outer core granules were filled in the hopper and its flow was adjusted. Already compressed inner core tablets were placed in the lower hopper. The speed of the tablet sonicator was adjusted to make a uniform flow of inner core tablets through the PVC tube of the tablet machine leading into the turret. The weight and thickness of the double core were adjusted as the preset limits. Once the parameters are achieved, the compressed double core tablets were subjected to below mentioned tests.

Characterization of Flavoxate HCl double core tablets

The compressed double core tablets were subjected to various physical and chemical quality control tests including appearance, diameter, hardness, thickness, weight variation, disintegration, and dissolution by standard procedures given in British Pharmacopeia (12).

In vitro dissolution studies

In-vitro release performance of the drug was determined by using the USP dissolution apparatus-II (Agilent, 708-DS, Germany). The dissolution medium (900 mL) was stirred at 100 rpm and the temperature was maintained at 37 ± 0.5°C. The dissolution of double core tablets was performed in 0.1 N HCl for 2 h and then in phosphate buffer pH 7.4 for further

Table 2. Composition of outer core batches with Povidone K-30.

Formulation composition	OCG _{WG} -I	OCG _{WG} -II	OCG _{WG} -III
Flavoxate HCl (mg)	100	100	100
Povidone K-30 (mg)	9	15	20
Avicel PH 101 (mg)	283	277	272
Magnesium Stearate (mg)	4	4	4
Aerosil (mg)	4	4	4
Total weight (mg)	400	400	400

22 h (total time 2 + 22 h = 24 h). The sample was withdrawn initially at 30 min and then after 1 and 2 h with the help of auto sampler. The solution was filtered using a 0.22 µm membrane filter and 5 ml of this solution was transferred to a 100 ml volumetric flask. The absorbance of the solution was measured at a wavelength of 292 nm using 0.1 N HCl solution as a blank. The absorbance of Flavoxate HCl standard solution was also measured at a wavelength of 292 nm. The percent of Flavoxate HCl released in the dissolution medium was calculated using the following formula (12).

$$\text{Percentage release of FLV HCL per tablet} = \frac{A_s}{A_{st}} \times \frac{W_{st}}{D_{st}} \times \frac{900}{1} \times \frac{100}{5} \times \frac{C}{600} \quad (1)$$

Where, A_s = absorbance of sample solution, A_{st} = absorbance of standard solution, W_{st} = weight of working standard, D_{st} = dilution of standard, 1 = number of tablets used, 600 = mg of Flavoxate HCl per tablet, C = % age potency of standard of Flavoxate HCl.

After 2 h, the tablets were transferred in phosphate buffer pH 7.4 medium previously maintained at a temperature of $37 \pm 0.5^\circ\text{C}$. Dissolution was performed for 22 h with paddle speed kept at 100 rpm. Samples were drawn at 4, 8, 12, 16, and 24 h, and

the absorbance was noted at a wavelength of 292 nm. The percent of Flavoxate HCl released was computed using Eq. 1.

Stability testing

Stability testing was carried out on two successful batches, i.e., one manufactured with HPMC and the other with Kollidon SR in accelerated conditions of temperature ($40 \pm 2^\circ\text{C}$) and relative humidity ($75 \pm 5\%$). The batches were tested for appearance, loss on drying, average weight, disintegration, *in-vitro* dissolution, and determination of related substance (3-methylflavone-8-carboxylic acid) at 0, 1, 2, 3 and 6 months. TLC method was performed for determination of related substances (16). All the results are presented as the mean $\pm$ standard deviation. Statistical analysis was carried out by using MS excel 2010.

RESULTS

Physical characteristics of Flavoxate HCl inner core granules with HPMC K15 and Kollidon SR

Physical characteristics of inner core granules with HPMC K15 and Kollidon SR are summarized in Table 3. The appearance of all granules shows uniform white texture without any agglomeration. The

Table 3. Physical characteristics of Flavoxate HCl inner core granules with HPMC K15 and Kollidon SR.

Formulation code	%Fines below 60 No. Mean $\pm$ SD	Bulk density Mean $\pm$ SD	Tapped density Mean $\pm$ SD	% Volume decrease	Hausner Ratio	LOD Mean $\pm$ SD
ICG _{WG-H} -I	64 $\pm$ 1.16	0.55 $\pm$ 0.01	0.66 $\pm$ 0.04	120	0.83	2.51 $\pm$ 0.01
ICG _{WG-K} -I	78 $\pm$ 0.95	0.64 $\pm$ 0.01	0.75 $\pm$ 0.01	117.19	0.85	2.49 $\pm$ 0.06
ICG _{WG-H} -II	67 $\pm$ 0.94	0.59 $\pm$ 0.01	0.68 $\pm$ 0.03	115.25	0.87	2.68 $\pm$ 0.01
ICG _{WG-K} -II	75 $\pm$ 0.99	0.61 $\pm$ 0.01	0.74 $\pm$ 0.01	121.31	0.82	2.58 $\pm$ 0.08
ICG _{WG-H} -III	69 $\pm$ 0.88	0.60 $\pm$ 0.01	0.69 $\pm$ 0.01	115	0.87	2.59 $\pm$ 0.01
ICG _{WG-K} -III	71 $\pm$ 0.99	0.60 $\pm$ 0.01	0.71 $\pm$ 0.01	118.33	0.85	2.58 $\pm$ 0.04
ICG _{WG-H} -IV	70 $\pm$ 0.85	0.61 $\pm$ 0.01	0.71 $\pm$ 0.03	116.39	0.86	2.61 $\pm$ 0.01
ICG _{WG-K} -IV	69 $\pm$ 0.71	0.65 $\pm$ 0.01	0.70 $\pm$ 0.01	107.69	0.93	2.58 $\pm$ 0.02
ICG _{WG-H} -V	67 $\pm$ 0.63	0.58 $\pm$ 0.01	0.66 $\pm$ 0.01	113.79	0.88	2.58 $\pm$ 0.02
ICG _{WG-K} -V	65 $\pm$ 0.99	0.56 $\pm$ 0.01	0.70 $\pm$ 0.01	125.00	0.80	2.52 $\pm$ 0.04
ICG _{WG-H} -VI	70 $\pm$ 0.67	0.56 $\pm$ 0.01	0.69 $\pm$ 0.04	123.21	0.81	2.52 $\pm$ 0.01
ICG _{WG-K} -VI	68 $\pm$ 0.74	0.56 $\pm$ 0.01	0.70 $\pm$ 0.01	125.00	0.80	2.56 $\pm$ 0.05
ICG _{WG-H} -VII	68 $\pm$ 0.97	0.56 $\pm$ 0.01	0.71 $\pm$ 0.04	126.79	0.79	2.55 $\pm$ 0.01
ICG _{WG-K} -VII	70 $\pm$ 0.97	0.58 $\pm$ 0.01	0.69 $\pm$ 0.01	118.97	0.84	2.49 $\pm$ 0.02
ICG _{WG-H} -VIII	69 $\pm$ 0.82	0.55 $\pm$ 0.01	0.68 $\pm$ 0.01	123.64	0.81	2.56 $\pm$ 0.01
ICG _{WG-K} -VIII	68 $\pm$ 0.67	0.58 $\pm$ 0.01	0.72 $\pm$ 0.01	124.14	0.81	2.58 $\pm$ 0.03
ICG _{WG-H} -IX	68 $\pm$ 0.79	0.56 $\pm$ 0.01	0.71 $\pm$ 0.05	126.79	0.79	2.49 $\pm$ 0.02
ICG _{WG-K} -IX	67 $\pm$ 0.70	0.49 $\pm$ 0.01	0.68 $\pm$ 0.01	138.78	0.72	2.61 $\pm$ 0.04

*(Where WG-H and WG-K represents wet granulation with HPMC K15 and wet granulation Kollidon SR, respectively)

sieve analysis result showed that the percentage of fine below sieve No. 60 is within acceptable limits. The percentage volume decrease was found above 100% in all cases. Similarly, Hausner ratio values showed better flow and compression properties for both types of granules. The granules prepared from HPMC K15 and Kollidon SR showed comparable bulk characteristics. All formulations have shown percent weight loss (LOD) between 2.49-2.68%, which signifies the presence of moisture for better compression and consolidation properties of inner core granules.

Thermal characterization of inner core

As per literature, Flavoxate HCl has a melting point of around 232-234°C and the presence of a single endothermic peak at a melting point is indicative of no polymorphic transition (17). DSC thermogram (Fig. 1) of inner core granules showed a sharp endothermic peak at around 234°C-237°C corresponding to the melting point of the drug. Both thermograms (HPMC K15 and Kollidon SR inner core granules) displayed shallow endothermic peaks above 100°C which can be attributed to the loss of moisture. These results are consistent with the LOD results as presented in Table 3.

FTIR analysis of inner core granules

Figure 2 shows a comparison of the FTIR spectra of inner core granules prepared with HPMC K15 and Kollidon SR with pure drugs. FTIR spectra of the pure drug showed all the principal peaks of Flavoxate HCl as per literature (18). The major peaks at 1717 cm^{-1} and 1205 cm^{-1} are attributed to C=O ester and C-N stretching band. Moreover, the HPMC K15 and Kollidon SR granules spectrum showed characteristic ester C=O and C-N stretching bands of pure drug confirming the lack of chemical interaction between drug and polymer.

The results of content uniformity were found to be in the range of 99.1-100.12% as given in Table 4.

Characterization of inner core tablets

The results of the physical characterization of all the batches prepared from HPMC K15 and Kollidon SR are given in Table 4. The appearance of tablets from all batches was uniform having white to off white color. The friability of all the batches was found to be in the range of $0.18 \pm 0.16\%$ to $0.88 \pm 0.01\%$. The hardness was found to be in the range of 5.11 ± 0.06 kP to 7.56 ± 0.36 kP. The weight variation of all the tablets was within the limits, i.e., <5%.

Figure 1. DSC thermogram for Flavoxate HCl inner core granules with HPMC K15 (A), DSC thermogram for Flavoxate HCl inner core granules with Kollidon (B).

Figure 2. Comparison of ATR Spectra of HPMC K15 and Kollidon SR granules with pure drug.

Table 4. Physical properties of Flavoxate HCl inner core tablet with HPMC K15.

Formulation code	Content uniformity of blend Mean ± SD	Diameter (mm) Mean ± SD	Friability (%)	Hardness (kP) Mean ± SD	Thickness (mm) Mean ± SD	Average weight Mean ± SD
ICT _{WG-H} -I	99.12 ± 0.56	12.01 ± 0.01	0.83 ± 0.13	5.17 ± 0.17	5.33 ± 0.03	590 ± 0.69
ICT _{WG-K} -I	99.32 ± 0.07	12.01 ± 0.01	0.88 ± 0.01	5.11 ± 0.06	5.44 ± 0.03	590 ± 0.81
ICT _{WG-H} -II	99.51 ± 0.26	12.01 ± 0.01	0.82 ± 0.28	5.71 ± 0.22	5.37 ± 0.10	610 ± 0.78
ICT _{WG-K} -II	99.43 ± 0.03	12.01 ± 0.01	0.75 ± 0.12	6.25 ± 0.12	5.42 ± 0.02	591 ± 0.99
ICT _{WG-H} -III	100.12 ± 0.53	12.01 ± 0.01	0.75 ± 0.33	5.79 ± 0.14	5.40 ± 0.11	640 ± 0.76
ICT _{WG-K} -III	99.43 ± 0.08	12.01 ± 0.01	0.74 ± 0.15	6.13 ± 0.05	5.40 ± 0.02	593 ± 0.94
ICT _{WG-H} -IV	99.61 ± 0.29	12.01 ± 0.01	0.55 ± 0.69	6.06 ± 0.32	5.42 ± 0.07	650 ± 0.91
ICT _{WG-K} -IV	99.45 ± 0.04	12.01 ± 0.01	0.43 ± 0.18	7.56 ± 0.36	5.46 ± 0.03	592 ± 0.98
ICT _{WG-H} -V	99.82 ± 0.25	12.01 ± 0.01	0.41 ± 0.52	6.28 ± 0.50	5.48 ± 0.12	655 ± 0.80
ICT _{WG-K} -V	99.95 ± 0.10	12.01 ± 0.01	0.18 ± 0.16	7.52 ± 0.04	5.53 ± 0.04	592 ± 0.93
ICT _{WG-H} -VI	100.23 ± 0.21	12.01 ± 0.01	0.38 ± 0.43	6.52 ± 0.26	5.45 ± 0.05	660 ± 0.80
ICT _{WG-K} -VI	100.12 ± 0.08	12.01 ± 0.01	0.21 ± 0.19	7.55 ± 0.10	5.42 ± 0.02	591 ± 0.95
ICT _{WG-H} -VII	99.88 ± 0.25	12.01 ± 0.01	0.34 ± 0.22	7.09 ± 0.26	5.47 ± 0.13	650 ± 0.92
ICT _{WG-K} -VII	99.38 ± 0.10	12.01 ± 0.01	0.24 ± 0.36	7.34 ± 0.63	5.41 ± 0.03	592 ± 0.81
ICT _{WG-H} -VIII	99.67 ± 0.30	12.01 ± 0.01	0.27 ± 0.29	7.18 ± 0.27	5.48 ± 0.12	655 ± 0.88
ICT _{WG-K} -VIII	99.58 ± 0.05	12.01 ± 0.01	0.22 ± 0.26	7.56 ± 0.10	5.44 ± 0.03	592 ± 0.95
ICT _{WG-H} -IX	99.19 ± 0.18	12.01 ± 0.01	0.25 ± 0.47	7.44 ± 0.46	5.50 ± 0.12	660 ± 0.78
ICT _{WG-K} -IX	99.69 ± 0.03	12.01 ± 0.01	0.23 ± 0.27	7.73 ± 0.16	5.44 ± 0.03	592 ± 0.73

Table 5. Physical properties Flavoxate HCl outer core granules.

Formulation code	Flavoxate HCl content Mean ± SD	Fines below 60 No. Mean ± SD	Bulk Density Mean ± SD	Tapped density Mean ± SD	Loss on Drying Mean ± SD
OCG _{WG} -I	99.10 ± 0.51	54 ± 0.01	0.54 ± 0.02	0.71 ± 0.02	2.61 ± 0.01
OCG _{WG} -II	100.12 ± 0.79	61 ± 0.02	0.56 ± 0.03	0.69 ± 0.06	2.55 ± 0.01
OCG _{WG} -III	99.25 ± 0.60	65 ± 0.01	0.59 ± 0.02	0.65 ± 0.06	2.53 ± 0.02

Physical characteristics of outer core granules

Three different outer core immediate release batches of Flavoxate HCl were prepared and results of physical properties are presented in Table 5. Sieve Analysis of all batches showed the percentage of fine below sieve No. 60 within 54 ± 0.01% to 65 ± 0.01%. The LOD values ranged from

2.53 ± 0.02% to 2.61 ± 0.01% for three outer core batches.

Thermal analysis of outer core granules

DSC thermogram of outer core granules (Fig. 3) shows a short endothermic peak at 243°C which represents the melting of the drug. There is a shallow

Figure 3. DSC thermogram and ATR for Flavoxate HCl outer core granules.

Table 6. Physical properties of Flavoxate HCl double core tablets with HPMC K15.

Formulation Code	Diameter (mm) Mean $\pm$ SD	Hardness (kP) Mean $\pm$ SD	Thickness (mm) Mean $\pm$ SD	Average weight (mg) Mean $\pm$ SD	Disintegration time (min) Mean $\pm$ SD
DCT _{H-WG} -I	16.01 $\pm$ 0.01	11.20 $\pm$ 0.24	6.32 $\pm$ 0.04	990.71 $\pm$ 0.42	10.50 $\pm$ 0.28
DCT _{K-WG} -I	16.01 $\pm$ 0.01	10.14 $\pm$ 0.08	6.39 $\pm$ 0.04	990.21 $\pm$ 0.35	10.40 $\pm$ 0.35
DCT _{H-WG} -II	16.01 $\pm$ 0.01	10.85 $\pm$ 0.09	6.35 $\pm$ 0.02	1011.59 $\pm$ 0.69	11.00 $\pm$ 0.39
DCT _{K-WG} -II	16.01 $\pm$ 0.01	10.82 $\pm$ 0.05	6.39 $\pm$ 0.04	992.21 $\pm$ 0.91	10.50 $\pm$ 0.21
DCT _{H-WG} -III	16.01 $\pm$ 0.01	11.80 $\pm$ 0.09	6.38 $\pm$ 0.03	1040.51 $\pm$ 0.69	11.20 $\pm$ 0.43
DCT _{K-WG} -III	16.01 $\pm$ 0.01	10.81 $\pm$ 0.05	6.39 $\pm$ 0.04	991.41 $\pm$ 0.35	10.20 $\pm$ 0.17
DCT _{H-WG} -IV	16.01 $\pm$ 0.01	11.66 $\pm$ 0.19	6.42 $\pm$ 0.01	1051.81 $\pm$ 0.82	10.30 $\pm$ 0.25
DCT _{K-WG} -IV	16.01 $\pm$ 0.01	11.36 $\pm$ 0.09	6.40 $\pm$ 0.03	990.26 $\pm$ 0.73	10.30 $\pm$ 0.25
DCT _{H-WG} -V	16.02 $\pm$ 0.02	12.14 $\pm$ 0.13	6.31 $\pm$ 0.04	1055.09 $\pm$ 0.74	10.40 $\pm$ 0.49
DCT _{K-WG} -V	16.02 $\pm$ 0.04	11.57 $\pm$ 0.08	6.40 $\pm$ 0.02	993.34 $\pm$ 0.85	10.50 $\pm$ 0.23
DCT _{H-WG} -VI	16.01 $\pm$ 0.01	12.48 $\pm$ 0.11	6.42 $\pm$ 0.01	1060.74 $\pm$ 0.91	10.50 $\pm$ 0.38
DCT _{K-WG} -VI	16.01 $\pm$ 0.01	11.63 $\pm$ 0.17	6.42 $\pm$ 0.01	991.23 $\pm$ 0.15	11.50 $\pm$ 0.18
DCT _{H-WG} -VII	16.01 $\pm$ 0.01	12.41 $\pm$ 0.41	6.45 $\pm$ 0.03	1054.90 $\pm$ 0.84	11.10 $\pm$ 0.55
DCT _{K-WG} -VII	16.01 $\pm$ 0.01	11.59 $\pm$ 0.03	6.39 $\pm$ 0.04	991.35 $\pm$ 0.65	11.00 $\pm$ 0.26
DCT _{H-WG} -VIII	16.01 $\pm$ 0.01	12.74 $\pm$ 0.03	6.47 $\pm$ 0.02	1059.47 $\pm$ 0.56	11.00 $\pm$ 0.47
DCT _{K-WG} -VIII	16.01 $\pm$ 0.01	11.62 $\pm$ 0.31	6.44 $\pm$ 0.02	992.25 $\pm$ 0.82	11.30 $\pm$ 0.41
DCT _{H-WG} -IX	16.01 $\pm$ 0.01	12.85 $\pm$ 0.08	6.48 $\pm$ 0.02	1060.94 $\pm$ 0.92	11.10 $\pm$ 0.53
DCT _{K-WG} -IX	16.01 $\pm$ 0.01	11.65 $\pm$ 0.17	6.46 $\pm$ 0.03	993.59 $\pm$ 0.76	11.10 $\pm$ 0.27

endotherm at 100°C representing moisture loss. These results agree with the DSC results of inner core granules.

FTIR analysis and content uniformity of Flavoxate HCl outer core granules

FTIR spectrum of outer granules (Fig. 3) displayed all the principal peaks of drugs which indicate that no interaction occurred between drug and polymer. Uniformity of content was performed for all the three Flavoxate HCl outer core granules by a validated HPLC method. The results indicated that peak area of standard preparation corresponds to that of sample preparation. The results of the content uniformity test (Table 5) were found to be in between 99.10 $\pm$ 0.51 to 100.12 $\pm$ 0.79%.

Physical characteristics of Flavoxate HCl double core tablets with HPMC K15/Kollidon SR

Physical characteristics of all the double core Flavoxate HCl batches are given in Table 6. The appearance of double core Flavoxate HCl tablets was from white to off white plain tablets. The hardness was in the range of 10.14 $\pm$ 0.08 kP to 12.85 $\pm$ 0.08 kP. The average tablet weight was observed to be in the range of 990.21 $\pm$ 0.35 mg

to 1060.94 $\pm$ 0.92 mg, lying within the official BP limits (12). The disintegration time was observed to be in the range of 10.20 $\pm$ 0.17 min to 11.50 $\pm$ 0.18 min.

Dissolution studies for Flavoxate HCl double core tablets with HPMC K15 and Kollidon SR

The dissolution of Flavoxate HCl double core tablets with HPMC K15 and Kollidon SR was performed in dissolution media of 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4) and the results are given in Table 7 and 8 and Figure 4. Batch DCT_{H-WG}-I failed to sustain the release of the drug for 2 h in 0.1 N HCl. The *in-vitro* release data of the drug was fitted to various release kinetic models. Drug release data of swellable matrix system DCT_{H-WG}-I was best fitted according to Korsmeyer-Peppas model, while the release data for the other eight batches (DCT_{H-WG}-II to DCT_{H-WG}-IX) followed Weibull model (Fig. 4).

All the double core batches with Kollidon SR released the drug at various time intervals in a 7.4 pH phosphate buffer. The *in-vitro* release data were fitted to various kinetic models and all the batches (DCT_{K-WG}-IV to DCT_{K-WG}-IX) were observed to follow the Weibull model (Fig. 4).

Table 7. Percentage release of Flavoxate HCl double core tablets with HPMC K15.

Formulation Code	Dissolution profile of Flavoxate HCl tablets (Sustained release) in 0.1 N HCl			Dissolution profile of Flavoxate HCl tablets(Sustained release) in Phosphate Buffer 7.4				
	0.5hr	1.0hr	2.0hr	4hr	8hr	12hr	16hr	24hr
DCT _{H-WG} -I	13.28	50.55	99.19	-	-	-	-	-
DCT _{H-WG} -II	14.08	40.84	71.11	98.48	-	-	-	-
DCT _{H-WG} -III	13.15	30.37	45.16	85.31	97.62	-	-	-
DCT _{H-WG} -IV	14.01	28.31	38.43	75.41	89.42	99.29	-	-
DCT _{H-WG} -V	13.12	24.21	31.25	65.47	77.29	98.59	-	-
DCT _{H-WG} -VI	14.22	22.56	27.23	56.21	69.25	83.29	98.95	-
DCT _{H-WG} -VII	14.09	20.32	24.35	34.21	52.23	67.25	87.65	97.26
DCT _{H-WG} -VIII	13.97	16.25	19.59	29.36	39.29	57.36	78.23	83.99
DCT _{H-WG} -IX	14.05	17.21	20.35	33.26	48.47	62.53	81.39	98.51

Table 8. Percentage release of Flavoxate HCl double core tablets with Kollidon SR.

Formulation Code	Dissolution profile of Flavoxate HCl tablets (Sustained release) in 0.1 N HCl% released			Dissolution profile of Flavoxate HCl tablets (Sustained release) in Phosphate Buffer 7.4% released				
	0.5 hr	1.0 hr	2.0 hr	4 hr	8 hr	12 hr	16 hr	24 hr
DCT _{K-WG} -I	13.2	36.55	69.19	97.48	-	-	-	-
DCT _{K-WG} -II	13.1	32.31	61.19	98.48	-	-	-	-
DCT _{K-WG} -III	14.0	30.37	52.96	82.11	97.62	-	-	-
DCT _{K-WG} -IV	14.1	25.31	32.43	70.41	80.02	98.79	-	-
DCT _{K-WG} -V	13.1	22.21	26.19	55.77	67.29	87.59	99.25	-
DCT _{K-WG} -VI	14.1	21.06	25.95	52.35	65.76	83.29	99.05	-
DCT _{K-WG} -VII	13.29	18.32	22.18	34.21	48.23	59.15	87.26	96.23
DCT _{K-WG} -VIII	13.97	16.25	17.29	25.95	42.73	54.26	72.36	82.99
DCT _{K-WG} -IX	14.15	17.42	20.87	32.17	45.77	58.29	78.36	98.51

Figure 4. A) Percentage drug release versus time for swellable Flavoxate HCl double core tablets with Kollidon SR B) Percentage drug release versus time for swellable double core Flavoxate HCl tablet with HPMC K15 C) Percentage drug release versus time for swellable Flavoxate HCl double core tablets prepared with Kollidon SR D) Percentage drug release versus time for swellable Flavoxate HCl double core tablets with HPMC K15.

Table 9. Stability studies of batches DCT_{H-WG}-IX and DCT_{K-WG}-IX prepared with HPMC K15 and Kollidon SR.

Test	Initial	40 ± 2°C/ RH 75 ± 5%				Initial	40 ± 2°C/RH 75 ± 5%			
		1	2	3	6		1	2	3	6
Dissolution 0.5 h	13.78	13.19	13.75	14.54	14.13	10.30	10.50	10.5	12.50	17.0
1 h	18.17	18.83	19.51	19.77	19.91	13.78	13.61	13.92	14.13	13.50
2 h	23.32	24.16	24.23	24.97	25.06	17.32	17.31	17.89	17.21	20.85
4 h	33.15	33.57	33.61	34.18	35.42	22.33	23.95	21.64	22.24	26.47
8 h	47.26	47.87	48.21	49.09	49.36	30.36	31.09	32.39	31.87	37.86
12 h	63.24	63.46	63.88	64.39	64.46	42.69	42.37	42.08	41.25	51.64
16 h	80.33	80.81	81.97	82.67	83.37	61.33	61.64	60.21	60.39	68.81
24 h	100.4	99.76	99.86	89.46	90.19	74.86	73.23	74.01	71.37	87.89
Assay by HPLC Each tablet contains Flavoxate HCl (600 mg)	101.82	100.10	100.55	99.78	95.42	101.57	101.69	100.15	98.86	95.05

Stability of selected double core formulations

From the swellable matrix tablets, two tablets, i.e., DCT_{H-WG}-IX, prepared with HPMC K15 and DCT_{K-WG}-IX, prepared with kollidon SR were selected based on *in-vitro* release data to perform accelerated stability studies. The two above-stated batches gave desirable release at the time points set for sampling. The stability studies were carried out as per ICH guidelines (16). The drug release of stability samples was comparable to that of the initial samples. The results of the stability studies are given in Table 9.

DISCUSSION

To improve patient compliance, differential release tablets are one of the important innovations in the delivery of drugs where multiple dosing is required. Dual-core tablets serve the purpose quite well, where outer layer release loading dose to achieve effective plasma concentration and inner sustained-release core gives plasma concentration over a prolonged period. In this study, dual-core tablets of Flavoxate HCl as a model drug consisting of an inner sustained-release core and outer immediate-release layer were prepared. The granules of the inner core were formulated with HPMC K15 and Kollidon SR which were apparently white in color, without any agglomeration. It was observed that the bulk and flow properties of inner core granules were dependent on the ratio of both polymers. Batches VII, VIII, and IX showed good flow and compressional properties where higher concentrations of polymers were used. Another important requirement was the lack of chemical interaction among excipients. In our studies, FTIR data

exhibited that there was no such interaction. DSC data confirmed the thermal stability of the drug. Inner core granules prepared from both HPMC K15 and Kollidon were subjected to compression into inner core tablets having optimum physical characteristics.

Outer core granules containing Flavoxate HCl were formulated by wet granulation technique using Povidone K30 as a binder. Micromeritic and compressional properties of these granules play a vital role as this layer is compressed on the inner core tablets. After performing the preliminary micromeritics studies, batch OCG_{WG}-II containing a moderate amount of binder was found to be the most appropriate one for double-core compression. Similarly, FTIR analysis of the double core tablets confirmed the absence of any interactions between excipients and drug. All the physical parameters of double core tablets compressed by using OCG_{WG}-II, i.e., content uniformity, diameter, thickness, weight variation, and hardness were observed to be within the limits given in BP (12). All compressed double core tablets were then subjected to dissolution analysis at pH 1.2 initially. Batch DCT_{H-WG}-I released the entire drug at pH 1.2, whereas all other formulations sustained the release of the drug for more than 2 h. Batches DCT_{H-WG}-II and DCT_{H-WG}-III showed sustained drug release for 4 h and 8 h, respectively. While batches DCT_{H-WG}-IV and DCT_{H-WG}-V exhibited sustained drug release for up to 12 h. Though the batch DCT_{H-WG}-VII could sustain the drug release for 24 h yet showed higher release at 16 h than the stipulated release limits for sustained release dosage form (20). DCT_{H-WG}-VIII sustained the release of the drug for 24 h, but the release at 24 h was 83.99%, which was lesser than the set limit, i.e., should not

be lesser than 85% at this time interval. The double compressed tablet batch DCT_{H-WG}-IX effectively complied with all the parameters set for the sustained release formulations at various time intervals till 24 h. The best-fitted release kinetic model was selected based on the coefficient of regression R². DCT_{H-WG}-II to DCT_{H-WG}-IX was best described by the Weibull model. Batches prepared with Kollidon SR inner core showed different release profiles. Tablet batch DCT_{K-WG}-I and DCT_{K-WG}-II could sustain the release of the drug only for 4 h, while batches DCT_{K-WG}-III and DCT_{K-WG}-IV could sustain the release of the drug for 8 and 12 h, respectively. Formulation DCT_{K-WG}-V and DCT_{K-WG}-VI sustained the drug release till 16 h. Among all, batch DCT_{K-WG}-VIII showed the lesser release at 12 h and the release was 82.99% which is less than the pre-set limit (85%). The release profile of the batch DCT_{K-WG}-IX complied with all the parameters set at various time intervals. The release kinetics for all the batches prepared with Kollidon SR inner core was best described by the Weibull model.

Although the HPMC K15 batch DCT_{H-WG}-IX seemed appropriate among all the formulations in terms of the desired characteristics for a sustained release dosage form, however, the weight of the double core tablet was 1060 mg. Furthermore, the release of the drug over 24 h for HPMC K15 based batch DCT_{H-WG}-IX was higher than the set limits for dissolution. Whereas DCT_{K-WG}-IX formulated with Kollidon SR exhibits a better release profile over 24 h along with appropriate tablet weight.

The stability studies for the two double core tablet formulations, one manufactured with HPMC K15 inner core, DCT_{H-WG}-IX, and the other prepared with Kollidon SR inner core, DCT_{K-WG}-IX were selected for the accelerated stability studies performed at 40°C temperature and 75% RH, as per ICH guidelines. The tablet batches were blister packed using opaque white PVC with 25-micron aluminum foil and were placed in the stability chamber (HPP, Memmert, Germany). Testing was carried out at T0, T1, T2, T3, and T6. The parameters studied were physical appearance, moisture content, average weight, and drug content. The findings showed satisfactory results at T0, T1, T2, T3 time frames, but results at T6 showed a significant increase in the moisture content of both the batches. Furthermore, the assay of both tablet batches manufactured with HPMC K15 and Kollidon SR was 95.75% and 95.07%, respectively, which was within the limit for the release (NLT 95%). Impurities were found to be remarkably increased at the T6 stage in stability studies. The

average weight of the tablet remained within the specified limits. The release profile of the selected formulation was similar and followed the same kinetics model, i.e., Weibull, as discussed above in the characterization of double core tablets with HPMC K15 and Kollidon SR.

CONCLUSION

In this study, double core tablets of Flavoxate HCl containing sustained-release inner core and immediate release outer layer were prepared and characterized. The drug release from the inner core was sustained for a prolonged period using swellable polymers, i.e., HPMC K15 and Kollidon SR. It has been shown that a simple and reproducible compression method can be applied to prepare double core tablets having desired release characteristics of the drug.

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Conflict of interest

The authors declare no conflicts of interest.

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