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## EVALUATION OF PRELIMINARY TRIAL BATCHES OF FORMULATIONS CONTAINING ORAL HYPOGLYCEMIC DRUGS METFORMIN HYDROCHLORIDE AND CANAGLIFLOZIN

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### Keywords:

Canagliflozin, Release Retardants, Metformin, Oral hypoglycemic drugs, Drug, Polymer ratio

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**ABSTRACT:** The *in-vitro* drug release profile from a hydrophilic matrix tablet is influenced by the viscosity of the gel layer formed due to its polymer hydration, and it depends on various other physical properties like a drug: polymer ratio water-solubility and particle size of the drug, particle size and type of the polymer, type of diluents used, and temperature of media. The drug release profile of different formulations *i.e.*, C1 to C6 formulated by utilizing Hypromellose K4M, Hypromellose K15M and Hypromellose K100M Respectively. K4M, which is low viscosity polymer, shows a faster release at initial time points. Hypromellose polymer (K100M) is hydrophilic in nature, showing fast hydration and controlling the dissolution profile. The dissolution profile of batch C1 to C2 having drug (Metformin HCl): polymer ratio 1:0.25 and 1:0.5 gives little controlled release profiles of the drug in C1, C2. Hence, 1:0.5 drug (Metformin HCl) to HPMC K100M was used for further study. It had been observed that HPMC K15M and K4M could not retard the release rate sufficiently to get the active content release from the dosage form at a regulated rate but HPMC K100M could. Thus, high viscosity grade HPMC K100M was selected for the study. The active content released from the tablet is dependent on the viscosity. Polymer with higher viscosity prevents rapid release in the beginning but have no effect on the later stages of the release rate of active content.

**INTRODUCTION:** Bi-layer tablet is suitable for the sequential release of two drugs in combination, two incompatible substances, and sustained release tablets in which one layer is immediate release as initial dose and the second layer is the maintenance dose. There is various application of the bi-layer tablet, it consist of monolithic partially coated or multilayered matrices.

In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity <sup>1,2</sup>.

**MATERIALS AND METHODS:** Formulating batches containing HPMC of various grades of varying concentrations. The *in-vitro* drug release profile from a hydrophilic matrix tablet is influenced by the viscosity of the gel layer formed due to its polymer hydration. It depends on various other physical properties like drug: polymer ratio water-solubility and particle size of the drug, particle size and type of the polymer, type of diluents used, and temperature of media <sup>3,4</sup>. It was observed that the drug release retards as the

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viscosity of the polymer was increased, HPMC K100M is the grade with higher viscosity, and it retards the drug release to a greater extent. In

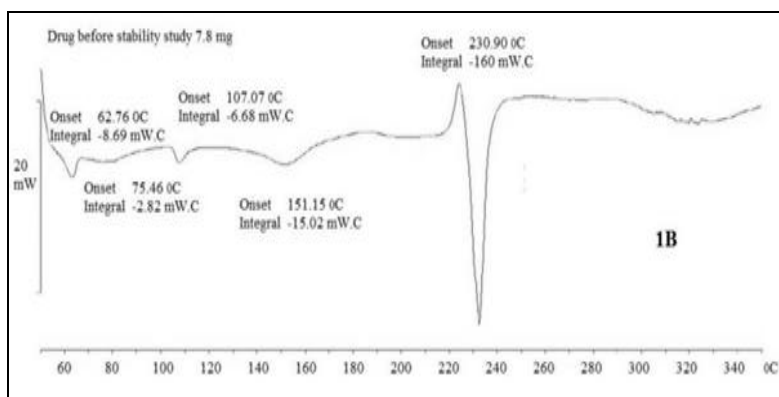
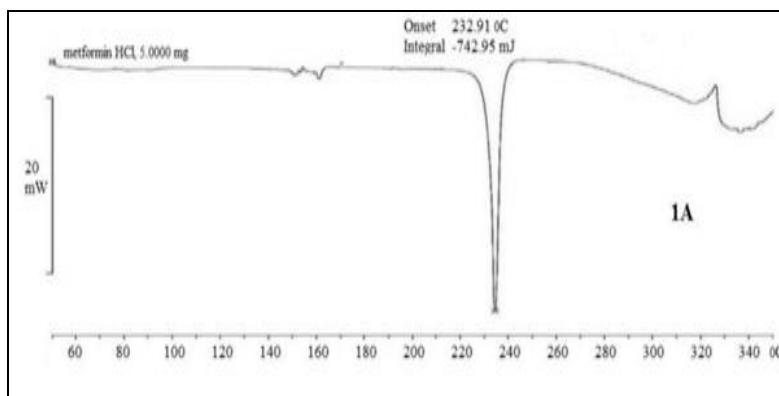
preliminary studies, different concentrations and various grades of HPMC K4M, HPMC K15M, and HPMC K100M were used in this study<sup>4,5</sup>.

**TABLE 1: FORMULATION OF BATCHES CONTAINING HPMC OF VARIOUS GRADES OF VARYING CONCENTRATIONS**

Ingredients (mg)	Batch No.					
	C1	C2	C3	C4	C5	C6
<b>Layer-SR</b>						
Metformin HCl	500.0	500.0	500.0	500.0	500.0	500.0
Hypromellose K 100M	80.0	160.0	-	-	-	-
Hypromellose K15M	-	-	80.0	160.0	-	-
Hypromellose K4M	-	-	-	-	80.0	160.0
Microcrystalline cellulose pH 102	204.0	124.0	204.0	124.0	204.0	124.0
Magnesium stearate	8.0	8.0	8.0	8.0	8.5	8.0
Talc	8.0	8.0	8.0	8.0	8.0	8.0
Total wt of SR layer (mg)						
<b>Layer-IR</b>						
Canagliflozin	50.0	50.0	50.0	50.0	50.0	50.0
Lactose	20.0	20.0	20.0	20.0	20.0	20.0
Microcrystalline cellulose pH 102	68	68	68	68	68	68
Kyron T-314	6.0	6.0	6.0	6.0	6.0	6.0
Talcum IP	2.0	2.0	2.0	2.0	2.0	2.0
Magnesium stearate IP	2.0	2.0	2.0	2.0	2.0	2.0
Iron oxide red	2.0	2.0	2.0	2.0	2.0	2.0
Total of IR layer (mg)	150.0	150.0	150.0	150.0	150.0	150.0
Total wt of bilayer tablet (mg)	950.0	950.0	950.0	950.0	950.0	950.0

**DSC Study:** DSC thermograms were recorded to study the thermal behavior of the drug. DSC thermogram of Canagliflozin along with excipients

and Metformin HCl along with excipients is shown in **Fig. 1** respectively.



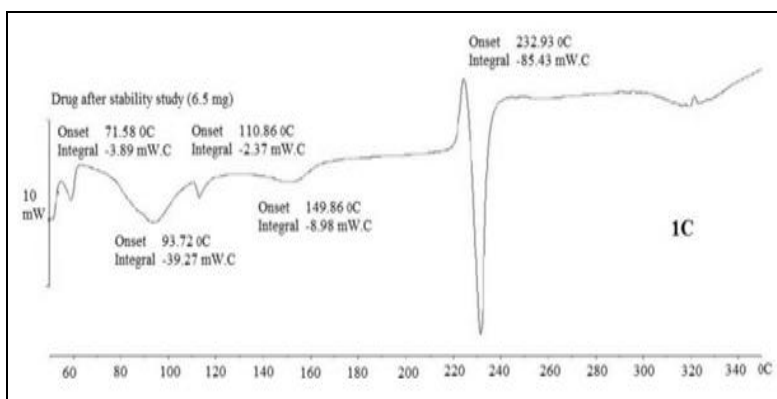


FIG. 1: DSC THERMOGRAMS OF METFORMIN HCL (1A), ITS MIXTURE WITH OTHER EXCIPIENTS BEFORE (1B) AND AFTER (1C) ACCELERATED STABILITY STUDIES

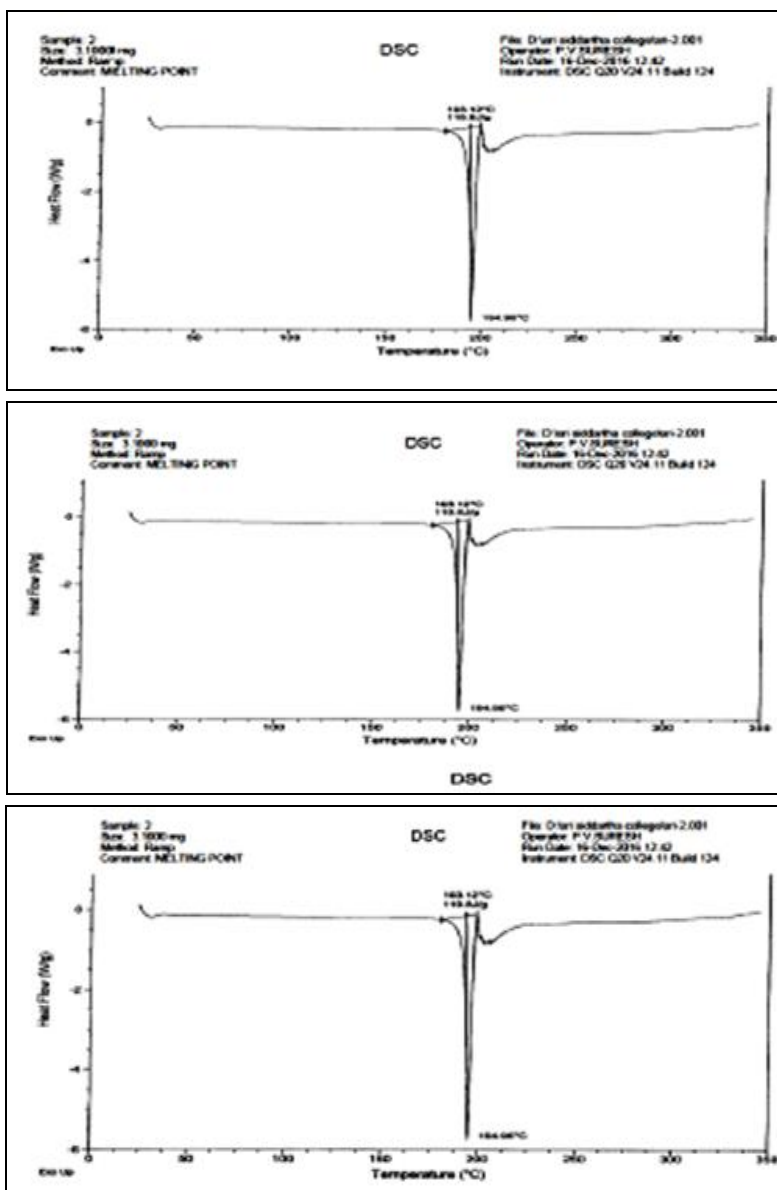
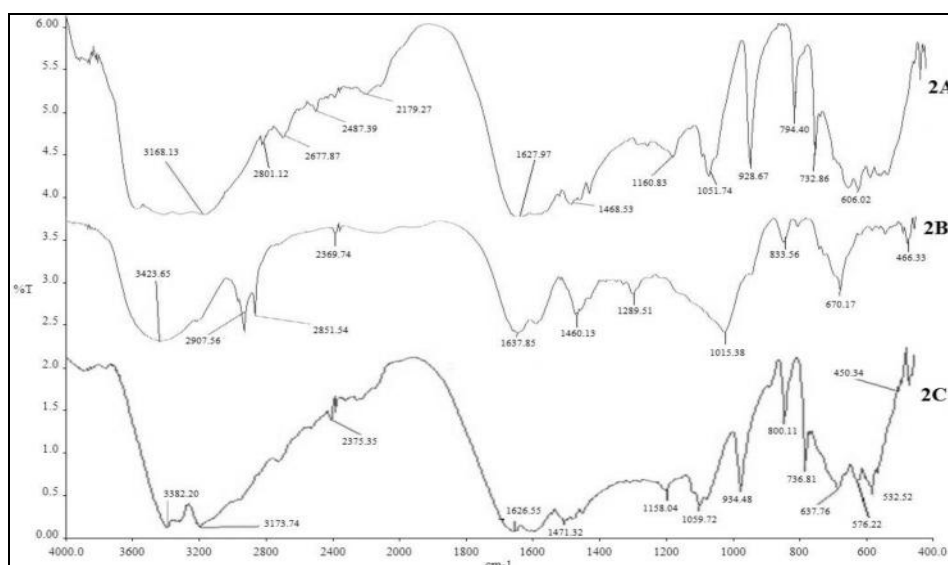


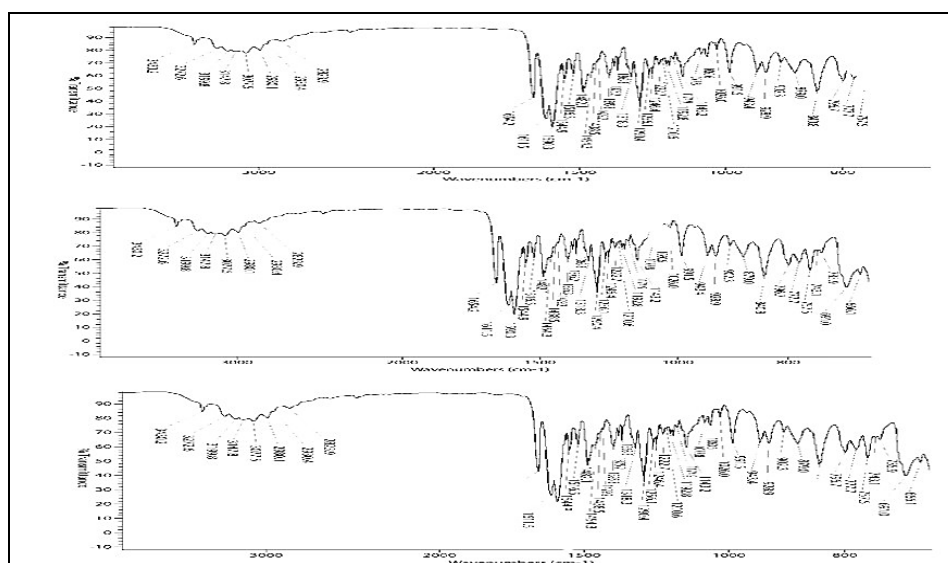
FIG. 2: DSC THERMOGRAMS OF CANAGLILOZIN AND ITS MIXTURE WITH OTHER EXCIPIENTS BEFORE AND AFTER (1C) ACCELERATED STABILITY STUDIES

**Fourier Transforms Infrared Spectroscopy:** As described in the methodology section, the Fourier transform infrared was conducted using drugs

metformin HCl and canagliflozin along with their selected excipients<sup>6,7</sup>. The results are summarized as follows.



**FIG. 3: FTIR SPECTRUM OF METFORMIN HCL (2A), ITS MIXTURE WITH OTHER EXCIPIENTS BEFORE (2B) AND AFTER (2C) ACCELERATED STABILITY STUDIES**



**FIG. 4: FTIR SPECTRUM OF CANAGLIFLOZIN, ITS MIXTURE WITH OTHER EXCIPIENTS BEFORE AND AFTER ACCELERATED STABILITY STUDIES**

The DSC thermograms of pure Metformin HCl and its physical mixture with other excipients (before and after accelerated stability studies) are shown in **Fig. 1**. Thermogram 1A exhibits a sharp endothermic peak at 232.91°C, which corresponds to the melting point of Metformin HCl. When Metformin HCl was mixed with other excipients, thermograms 1B and 1C still retained drug peak, which indicates Metformin HCl compatibility with other excipients used for the proposed formulation composition<sup>8-10</sup>.

Similarly, FTIR spectrum of pure Metformin HCl (2A) in **Fig. 3** exhibits entire characteristic peak N-H stretching, C = N stretching, C-N stretching, and C-H bending at 3168.19 cm<sup>-1</sup>, 1627.97 cm<sup>-1</sup>,

1051.74 cm<sup>-1</sup>, and 1468.53 cm<sup>-1</sup> respectively when compared with reported reference spectrum of the drug. These distinctive drug peaks were present in the FTIR spectrum of the physical mixture of the drug with other excipients before the accelerated stability study **Fig. 2B** and the optimized tablet after the accelerated stability study **Fig. 2C**. From the DSC and the FTIR studies, it can be concluded that Metformin HCl is highly compatible with other excipients used in the formulation<sup>11, 12</sup>.

The DSC thermograms of pure Canagliflozin its physical mixture with other excipients (before and after of accelerated stability studies) are shown in **Fig. 2**. Thermogram 1 exhibits a sharp endothermic peak at 190.12 for canagliflozin.

When canagliflozin mixed with other excipients, thermogram 3 still retained drug peak, which is the indication of canagliflozin compatibility with other excipients used for the proposed formulation composition<sup>13-15</sup>. Similarly, FTIR spectrum of pure Canagliflozin exhibits the peak C=N stretching, C-N stretching, and C-H bending at  $1590.3\text{cm}^{-1}$ ,  $1305.2\text{cm}^{-1}$  and  $991.5\text{cm}^{-1}$  respectively when compared with the reported reference spectrum of the drug<sup>16</sup>.

These distinctive drug peaks were present in the FTIR spectrum of the physical mixture of the drug with other excipients before the accelerated stability study **Fig. 4** and the optimized tablet after the accelerated stability study **Fig. 4C**.

From the DSC and the FTIR studies, it can be concluded that canagliflozin is compatible with other excipients used in the formulation.

**TABLE 2: CANAGLIFLOZIN WITH EXCIPIENTS**

Ingredients	Ratio	Physical description (initial)	Condition (40°C / 75%RH)			
			After one week	After two week	After three week	After four week
Canagliflozin + MCC	1:1	White powder	NCC	NCC	NCC	NCC
Canagliflozin + lactose	1:1	White powder	NCC	NCC	NCC	NCC
Canagliflozin + Kyron T-314	1:1	White powder	NCC	NCC	NCC	NCC
Canagliflozin +SSG	1:1	White powder	NCC	NCC	NCC	NCC
Canagliflozin +CCS	1:1	Cream to off White powder	NCC	NCC	NCC	NCC
Canagliflozin +Pregelatinized starch	1:1	white powder	NCC	NCC	NCC	NCC
Canagliflozin +talc	1:1	White powder	NCC	NCC	NCC	NCC
Canagliflozin +magnesium stearate	1:1	White powder	NCC	NCC	NCC	NCC
Canagliflozin + iron oxide Yellow	1:1	Yellow color powder	NCC	NCC	NCC	NCC

**TABLE 3: METFORMIN WITH EXCIPIENTS**

Ingredients	Ratio	Physical description (initial)	Condition (40°C / 75%RH)			
			After one week	After two week	After three week	After four week
Metformin HCl + MCC	1:1	Off White powder	NCC	NCC	NCC	NCC
Metformin HCl + lactose	1:1	White powder	NCC	NCC	NCC	NCC
Metformin HCl +HPMC K4 M	1:1	Cream to off white powder	NCC	NCC	NCC	NCC
Metformin HCl +HPMC K15 M	1:1	Cream to off white powder	NCC	NCC	NCC	NCC
Metformin HCl +HPMC K100 M	1:1	Cream to off white powder	NCC	NCC	NCC	NCC
Metformin HCl +Carbopol 934P	1:1	White powder	NCC	NCC	NCC	NCC
Metformin HCl +sodium bicarbonate	1:1	White powder	NCC	NCC	NCC	NCC
Metformin HCl +sodium carbonate	1:1	White powder	NCC	NCC	NCC	NCC
Metformin HCl +potassium carbonate	1:1	White powder	NCC	NCC	NCC	NCC
Metformin HCl +calcium carbonate	1:1	White powder	NCC	NCC	NCC	NCC
Metformin HCl +talc	1:1	white powder	NCC	NCC	NCC	NCC
Metformin HCl +magnesium stearate	1:1	white powder	NCC	NCC	NCC	NCC

NCC-No color change, Evaluation of Batches containing Various Grades of HPMC at Varying Concentrations in Canagliflozin with Metformin HCl.

**TABLE 4: POWDER BLEND PROPERTIES OF TRAIL BATCHES CONTAINING HPMC OF VARIOUS GRADES OF VARYING CONCENTRATIONS**

	Batch no	Bulk density (gm/cm <sup>3</sup> )	Tapped density (gm/cm <sup>3</sup> )	Angle of Repose (θ)	Carr's Index (%)	Hausner's ratio
Canagliflozin with metformin HCl	C1	0.41±0.01	0.52±0.04	26.32±1.2	20.1±1.2	1.31±0.32
	C2	0.47±0.02	0.57±0.02	26.24±1.3	23.1±1.4	1.28±0.01
	C3	0.43±0.04	0.53±0.02	25.43±1.6	18.9±1.3	1.31±0.04
	C4	0.42±0.02	0.51±0.04	27.24±1.4	21.1±1.2	1.29±0.03
	C5	0.46±0.01	0.54±0.03	27.31±1.1	22.3±1.3	1.23±0.02
	C6	0.44±0.02	0.56±0.01	26.31±1.3	19.4±1.1	1.26±0.01

Mean ± SD, n=3

**TABLE 5: PHYSICAL PARAMETERS OF TRAIL BATCHES CONTAINING HPMC OF VARIOUS GRADES OF VARYING CONCENTRATIONS**

	Batch No	Weight variation (mg)	Thickness (mm)	Friability (% w/w)	Hardness (kg/cm <sup>2</sup> )
Canagliflozin with metformin HCl	C1	949±0.63	6.6 ± 0.01	0.74±0.13	5.4±0.21
	C2	949±0.45	6.8 ± 0.04	0.65±0.14	5.3±0.23
	C3	946±0.51	6.8 ± 0.03	0.70±0.15	5.6±0.26
	C4	944±0.46	6.7 ± 0.04	0.72±0.12	5.2±0.21
	C5	951±0.49	6.8 ± 0.03	0.66±0.17	5.3±0.12
	C6	946±0.61	6.8 ± 0.01	0.69±0.04	5.3±0.14

**TABLE 6: % DRUG CONTENT OF CANAGLIFLOZIN AND METFORMIN HCL OF BATCHES C1-C6**

Batch No	% Drug content	
	Canagliflozin	Metformin HCl
C1	98.12±0.31	99.11±0.31
C2	98.96±0.64	98.98±0.62
C3	98.95±0.41	99.03±0.31
C4	99.11 ±0.49	98.72 ±0.52
C5	98.92±0.31	98.94±0.31
C6	96.69±0.31	99.36±0.32

**TABLE 7: IN-VITRO DISSOLUTION PROFILE DATA OF FORMULATIONS C1-C6**

Batch No.	C1	C2	C3	C4	C5	C6
<b>Cumulative % drug release (Canagliflozin)</b>						
5 min	52.21±0.53	53.48±0.31	59.11±0.53	54.71±0.52	62.61±0.64	64.64±0.43
10 min	91.54±0.43	88.46±0.11	90.24±0.33	91.24±0.41	88.73±0.21	90.04±0.31
15 min	97.14±0.32	93.13±0.12	95.59±0.62	96.65±0.23	95.76±0.27	96.49±0.54
20 min	98.74±0.22	95.86±0.33	97.61±0.22	97.71±0.83	97.71±0.14	97.53±0.11
30 min	99.83±0.19	99.93±0.24	99.91±0.24	99.92±0.21	98.93±0.49	98.91±0.22
<b>Cumulative % drug release (Metformin HCl)</b>						
0.5 hr.	20.59±0.11	13.23±0.21	26.31±0.24	22.59±0.23	28.11±0.23	26.33±0.21
1 hr.	31.32±0.27	20.17±0.26	36.27±0.12	33.17±0.17	38.94±0.12	35.18±0.24
2 hr.	42.54±0.13	29.64±0.12	46.68±0.13	41.97±0.23	48.21±0.25	40.08±0.19
3 hr.	52.92±0.27	43.62±0.14	59.65±0.22	56.43±0.25	61.26±0.12	55.23±0.15
4 hr.	63.24±0.23	54.26±0.13	66.47±0.23	63.37±0.13	74.12±0.17	61.12±0.21
6 hr.	76.94±0.14	66.32±0.15	74.01±0.21	71.58±0.20	79.69±0.21	70.58±0.18
8 hr.	80.79±0.21	72.28±0.23	82.6±0.26	80.82±0.11	81.87±0.18	80.22±0.13
10 hr.	85.67±0.12	82.95±0.24	-	84.12±0.17	-	84.43±0.21
12 hr.	-	-	-	-	-	-

Mean ± SD, n=3

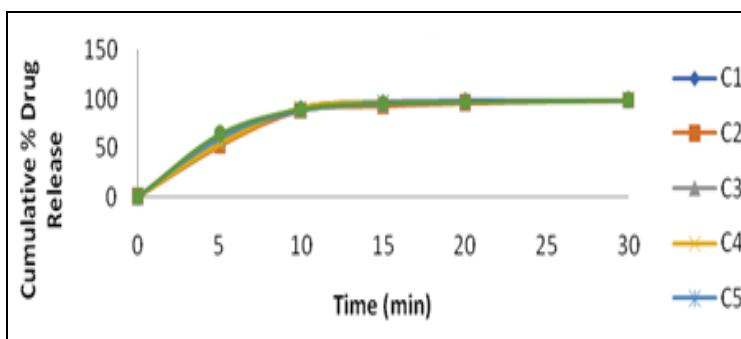


FIG. 5 (A): *IN-VITRO* DISSOLUTION OF CANAGLIFLOZIN IR LAYER OF BATCHES C1-C6(A)

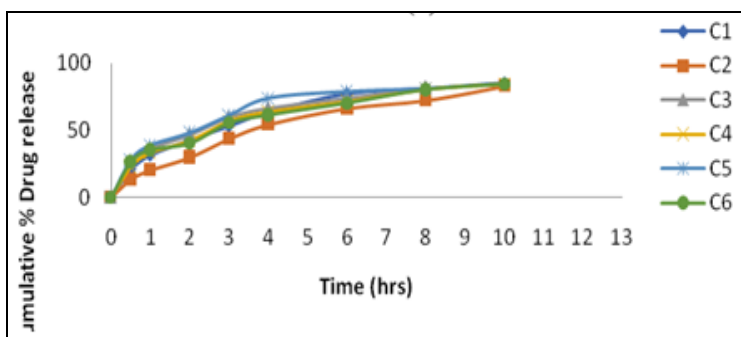


FIG. 5 (B): *IN-VITRO* DISSOLUTION OF METFORMIN HCL SR LAYER OF C1-C6(B)

FIG. 5: (A), (B): *IN-VITRO* DISSOLUTION PROFILE COMPARISON FOR RELEASE OF CANAGLIFLOZIN IR LAYER AND METFORMIN HCL SR LAYER BILAYER TABLETS USING HPMC K4M, HPMCK15M AND HPMC K100M AS POLYMER

**RESULTS & DISCUSSION:** Floating was not observed in any of the above-prepared trial batches. The drug release profile of different formulation *i.e.* C1 to C6 formulated by utilizing Hypromellose K4M, Hypromellose K15M and Hypromellose K100M, respectively. The dissolution profile shows biphasic active release with a rapid loading dose followed by slower release in another polymer-controlled phase. Due to the different viscosity grades of polymer utilized, differences in drug release were observed. The formulation where Hypromellose K4M is a low-viscosity polymer shows a faster release at initial time points.

Hypromellose polymer (K100M) is hydrophilic in nature, showing fast hydration and controlling the dissolution profile. The dissolution profile of batch C1 to C2 having drug (Metformin HCl): polymer ratio 1:0.25 and 1:0.5 gives little controlled release profiles of the drug in C1, C2. Hence, 1:0.5 drug (Metformin HCl) to HPMC K100M was used for further study. It had been observed that HPMC K15M and K4M could not retard the release rate sufficiently to get the active content release from the dosage form at a regulated rate, but HPMC K100M could. Thus, high viscosity grade HPMC K100M was selected for the study.

**CONCLUSION:** The tablet's active content release depends on the viscosity. Polymer with higher viscosity prevents the rapid release in the beginning but has no effect on the later stages of the release rate of active content.

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**CONFLICTS OF INTEREST:** There is no conflict of interest among the authors.

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