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EVALUATION OF BATCHES CONTAINING VARIOUS GRADES OF HPMC AT VARYING CONCENTRATIONS OF FLOATING BILAYERED TABLET CONTAINING METFORMIN HYDROCHLORIDE AND SGLT2 INHIBITOR

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1. INTRODUCTION

There are several types of gastro retentive system but among of all these system gastro retentive floating drug delivery system had major advantages. In this system the active content embedded in the dosage form and having a desired release mechanism with buoyancy on to the gastric fluid. This type of dosage form float in the gastric environment without effecting the gastric emptying rate and so the dosage form remain in the gastric environment for longer period of time. During the floating stage the active content release from the dosage form at specified time and rate in the gastric environment.[1]

Orally delivered biguanide for example Metformin Hydrochloride vastly utilized in the treatment of Non-Insulin Dependent Diabetes Mellitus. Metformin Hydrochloride improves insulin sensitivity in liver and muscle and so enhances glycemic control.[2] Orally delivered biguanide has application on cardiac disease like insulin resistance, fibrinolytic abnormalities and dyslipidemia etc.[3]

Metformin Hydrochloride have half-life of four hours to six hours which incompletely absorbed and excreted in the urine.[4] Metformin Hydrochloride is protonated under strong physiological condition its pKa is around 11.5 and is a strong base. The absorption pattern of Metformin Hydrochloride had been affected by negatively charged intestinal epithelium.[5] Metformin Hydrochloride has saturable dose dependent mechanism and its absorption is in the small intestine.[6]

A modified release dosage form generally release the active content in the colon. So as per this the absorption window should be in colon or throughout the complete gastrointestinal tract. Some scientist done research and concluded that absorption window of Metformin Hydrochloride is low in the colon. So if the Metformin Hydrochloride release in the small intestine has no pharmacological action and low therapeutic value. After the research it had been concluded that if the dosage form like gastro retentive tablets of Metformin Hydrochloride when administered there is sudden change in the mean bioavailability of Metformin Hydrochloride increase to 115 % which is quite high when compare to immediate release formulation of Metformin Hydrochloride.[7]

2. METHODOLOGY

2.1. PRELIMINARY TRIAL BATCHES OF FORMULATIONS –METFORMIN HCL /DAPAGLIFLOZIN IR LAYER

2.1.1. Formulation of batches containing HPMC of various grades of varying concentrations

Use of a hydrophilic polymer matrix system is one of the most popular approaches in formulating a controlled release dosage form. This is due to fact that these formulations are relatively flexible and a well-designed system usually gives reproducible release profile. There have been many studies demonstrating that 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. Also, it has been shown that it depend on various other factors like water-solubility and particle size of the drug, particle size and type of the polymer, type of diluents used, drug: polymer ratio and temperature of the release media. Many researchers have worked in formulation of bilayered tablets using different grades of HPMC like K4M, K15M, and K100M. It was observed that as the viscosity of polymer was increased, the retardation in the drug release was seen. HPMC K100M is the grade with higher viscosity and it retards the drug release to greater extent. Here in preliminary studies, we have checked for different concentrations of grades of HPMC K4M, HPMC K15M and HPMC K100.

Table 2.1.1 Drug and Excipients for the formulation of IR & SR Layer of Floating Drug Delivery.

Ingredients (mg)	Batch No.					
	B1	B2	B3	B4	B5	B6
Layer-SR						
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	8.0	8.0
Talc	8.0	8.0	8.0	8.0	8.0	8.0
Total wt of SR layer (mg)	800.0	800.0	800.0	800.0	800.0	800.0
Layer-IR						
Dapagliflozin	2.5	2.5	2.5	2.5	2.5	2.5
Lactose	20.0	20.0	20.0	20.0	20.0	20.0
Microcrystalline cellulose pH 102	115.5	115.5	115.5	115.5	115.5	115.5
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

Table 2.1.2 Drug Excipients compatibility studies.

Dapagliflozin with Excipients

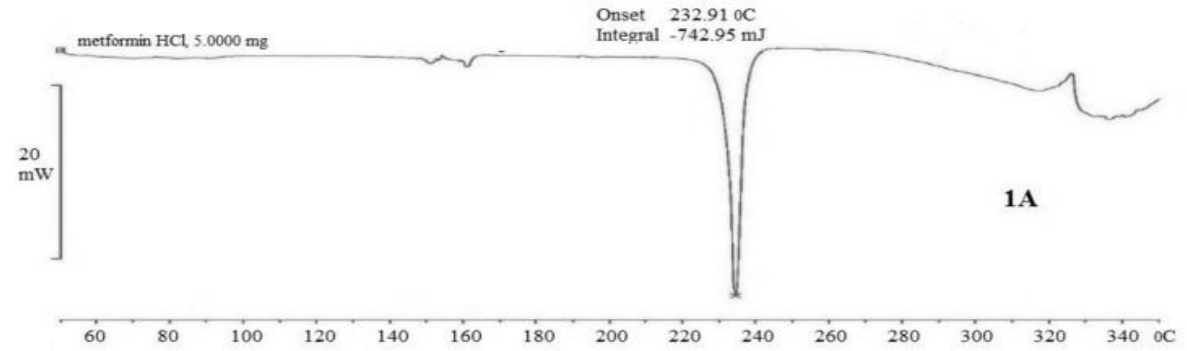
Ingredients	Ratio	Physical description (initial)	Condition (40°C / 75%RH)			
			After one week	After two week	After three week	After four week
Metformin HCl + MCC	1:1	Off White powder	NCC	NCC	NCC	NCC
Metformin HCl + lactose	1:1	White powder	NCC	NCC	NCC	NCC
Metformin HCl +HPMC K4 M	1:1	Cream to off white 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 +sodium bicarbonate	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

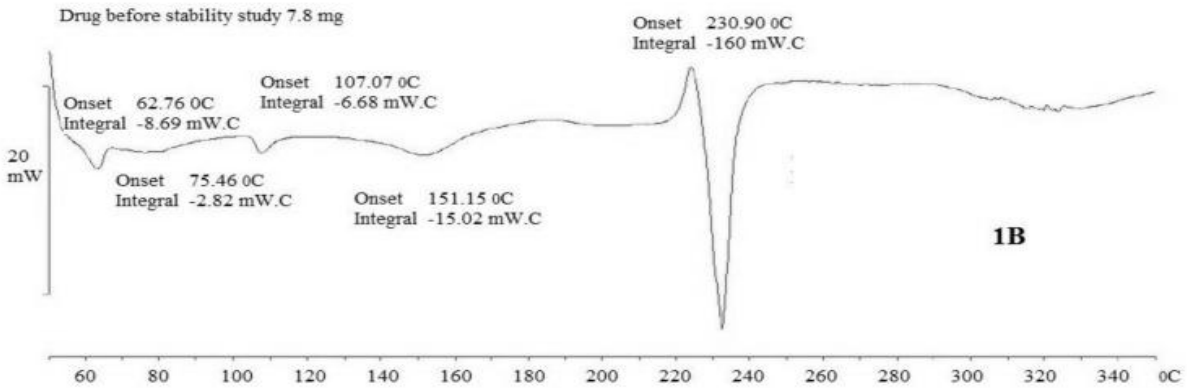
3. RESULTS AND DISCUSSION

The DSC thermograms of pure Metformin HCl, its physical mixture with other excipients

(before and after of accelerated stability studies) are shown in Figure 6.1.8. Thermograms 1A exhibit a sharp endothermic peak at 232.91°C which corresponds to melting point of Metformin HCl. When Metformin HCl was mixed with other Excipients, thermograms 1B and 1C still retained drug peak, which is the indication of Metformin HCl compatibility with other Excipients used for the proposed formulation composition.

Similarly, FTIR spectrum of pure Metformin HCl (2A) in Figure exhibits entire characteristic peak N-H stretching, C = N stretching, C-N stretching, and C-H bending at 3168.19 cm^{-1}, 1627.97 cm^{-1}, 1051.74 cm^{-1}, and 1468.53 cm^{-1} respectively when compared with reported reference spectrum of the drug. These distinctive drug peaks were present in FTIR spectrum of physical mixture of the drug with other excipients before the accelerated stability study (Figure 2B) and the optimized tablet after the accelerated stability study (Figure 2C) as well. From the DSC and the FTIR studies, it can be concluded that Metformin HCl is highly compatible with other excipients used in the formulation.





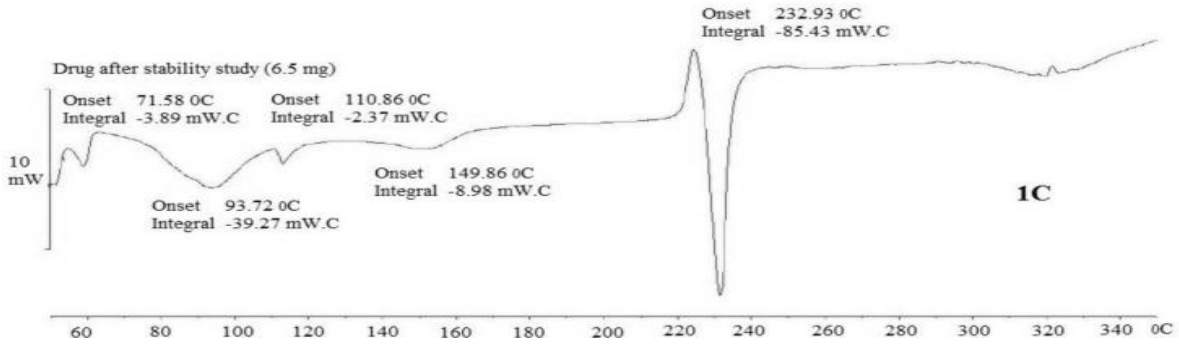


Fig.3.1.1 DSC thermograms of Metformin HCl (1A), its mixture with other excipients before (1B) and after (1C) accelerated stability studies.

Fourier transforms infrared spectroscopy

As described in the methodology section the Fourier transform infrared conducted using drugs Metformin HCl-Dapagliflozin along with their selected excipients. The results are summarized as follows.

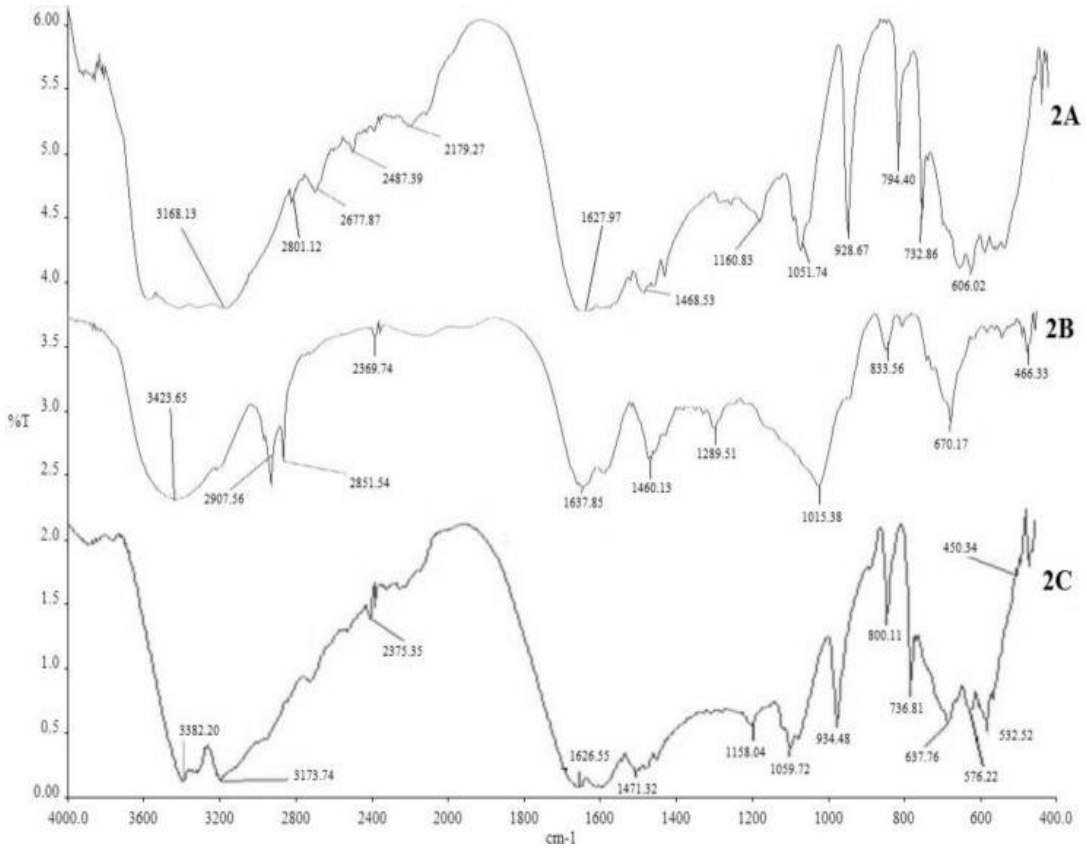


Fig.3.1.2 FTIR spectrum of Metformin HCl (2A), its mixture with other excipients before (2B) and after (2C) accelerated stability studies.

3.2 Evaluation of Batches containing Various Grades of HPMC at Varying Concentrations

Table 2.2. Powder blend properties of trail batches containing HPMC of various grades of varying concentrations.

	Batch no	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of Repose (θ)	Carr's Index(%)	Hausner's ratio
Dapagliflozin with metformin HCl	B1	0.42±0.02	0.53±0.01	25.49±1.2	18.2±1.3	1.24±0.02
	B2	0.41±0.01	0.58±0.0	26.39±1.6	21.5±1.6	1.19±0.03
	B3	0.47±0.04	0.51±0.02	25.68±1.3	19.8±1.2	1.20±0.02
	B4	0.43±0.01	0.52±0.02	27.16±1.2	20.3±1.1	1.26±0.04
	B5	0.44±0.02	0.53±0.01	27.35±1.6	21.2±1.4	1.25±0.01
	B6	0.42±0.01	0.55±0.03	26.11±1.6	18.5±1.7	1.24±0.03

Mean ± SD, n=3

Table 3.3. 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/cm2)
Dapagliflozin with metformin HCl	B1	951±0.61	6.7 ± 0.02	0.72±0.12	5.2±0.20
	B2	952±0.54	6.8 ± 0.01	0.66±0.18	5.3±0.16
	B3	948±0.91	6.8 ± 0.04	0.69±0.09	5.3±0.19
	B4	949±0.68	6.7 ± 0.02	0.72±0.18	5.4±0.20
	B5	952±0.96	6.8 ± 0.04	0.65±0.14	5.4±0.20
	B6	947±0.72	6.8 ± 0.03	0.70±0.16	5.6±0.26

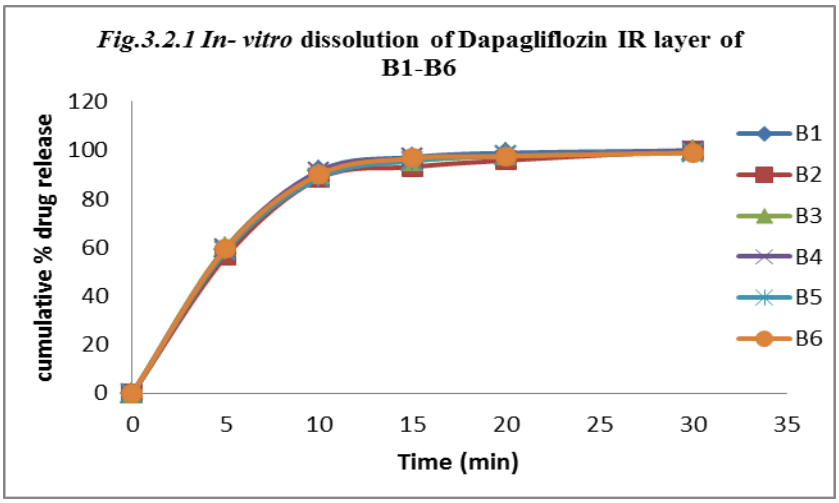
Table 3.4. % Drug content of Dapagliflozin and Metformin HCL of batches B1-B6.

Batch No	% Drug content	
	Dapagliflozin	Metformin HCl
B1	99.13 ±0.51	98.73 ±0.51
B2	98.95±0.36	98.95±0.36
B3	98.76±0.34	99.26±0.34
B4	99.10±0.41	99.10±0.41
B5	98.98±0.68	98.99±0.68
B6	98.95±0.41	99.01±0.38

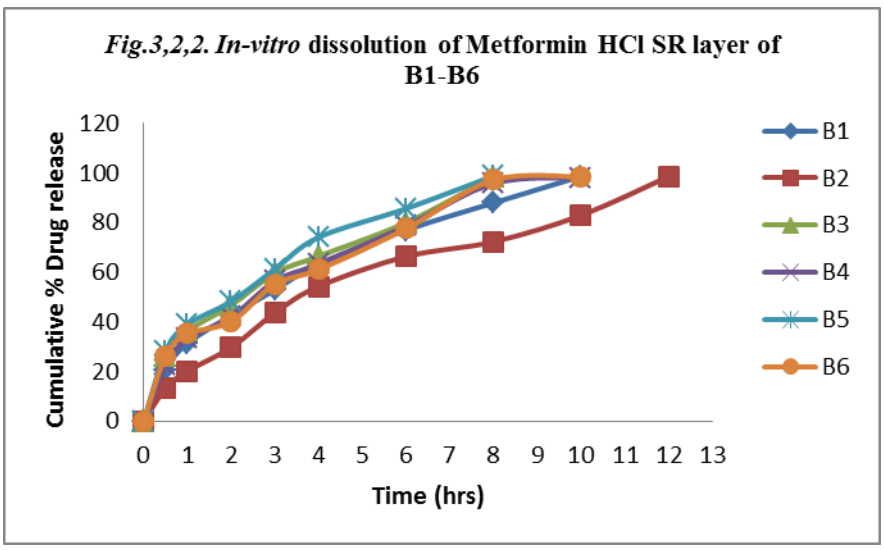
Table 3.5: *In-vitro* dissolution profile data of formulations B1-B6.

BATCH NO	B1	B2	B3	B4	B5	B6
Cumulative % drug release (Dapagliflozin)						
5 min	59.24±0.57	56.49±0.33	60.14±0.57	59.72±0.55	58.54±0.66	59.69±0.49
10 min	91.56±0.43	88.56±0.13	90.23±0.37	91.29±0.43	88.76±0.22	90.09±0.33
15 min	97.15±0.22	93.15±0.12	95.59±0.42	96.69±0.22	95.66±0.29	96.69±0.52
20 min	98.87±0.28	95.87±0.38	97.66±0.28	97.76±0.86	97.71±0.19	97.59±0.18

30 min	99.87±0.16	99.96±0.28	99.92±0.21	99.93±0.29	98.99±0.45	98.93±0.28
Cumulative % drug release (Metformin HCl)						
0.5 hr.	20.69±0.10	13.24±0.21	26.31±0.28	22.59±0.22	28.11±0.28	26.35±0.26
1 hr.	31.34±0.28	20.15±0.28	36.28±0.13	33.19±0.19	38.94±0.13	35.19±0.25
2 hr.	42.55±0.14	29.65±0.10	46.69±0.17	41.96±0.21	48.22±0.26	40.09±0.19
3 hr.	52.91±0.28	43.61±0.15	59.64±0.21	56.44±0.28	61.27±0.11	55.24±0.16
4 hr.	63.26±0.21	54.27±0.11	66.48±0.24	63.38±0.12	74.13±0.16	61.10±0.22
6 hr.	76.99±0.15	66.33±0.16	80.02±0.20	78.59±0.20	85.68±0.20	77.59±0.18
8 hr.	87.99±0.22	72.29±0.24	98.57±0.27	95.83±0.19	98.89±0.19	97.20±0.16
10 hr.	98.66±0.16	82.97±0.22	-	98.13±0.16	-	98.41±0.20
12 hr.	-	98.63±0.20	-	-	-	-
Mean ± SD, n=3						



(a)



(b)

Fig 3.2 (a), (b): *In- vitro* Dissolution profile comparison for release of Dapagliflozin IR layer and Metformin HCl SR layer Bilayered tablets using HPMC K4M, HPMCK15M and HPMC K100M as polymer.

Floating was not observed in any of the above prepared trail batches. The drug release profile of different formulation i.e. B1 to B6 formulated by utilizing Hypromellose K4M, Hypromellose K15M and Hypromellose K100M. The dissolution profile shows biphasic release of active with rapid loading dose followed by slower release in another phase which is controlled by polymer. Due to different viscosity grade of polymer utilized differences in drug release were observed. In the formulation where Hypromellose K4M utilized which is low viscosity polymer shows a faster release at initial time points. So by utilizing the Hypromellose polymer (K100M) which is hydrophilic in nature and showing fast hydration and controlling the dissolution profile.

Dissolution profile of batch: (B1 to B2) having drug (Metformin HCl): polymer ratio 1:0.25 and 1:0.5 gives good controlled release profiles of drug in B1,B2. 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 regulated rate but HPMC K100M could. Thus, high viscosity grade HPMC K100M was selected for study.

CONCLUSION

It can be concluded that viscosity is playing the major role in active content release from the tablets. The ingredient with high viscosity when utilized it prevents the initial rapid release of the drug but later on it does not have any effect on the release rate of the active content.

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