Development of Dapagliflozin Effervescent Floating Tablets

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***Abstract*-Dapagliflozin is a highly potent and reversible sodium-glucose cotransporter-2 (SGLT2) drug now being used for the treatment of Type 2 diabete (TD2M) that acts selectively on sodium-glucose cotransporter-2. Dapagliflozin can be used as mono-therapy or combination therapy as glucose-lowering agents for the treatment of T2DM. Either, it is taken once daily orally for its use as monotherapy in patients who are experiencing metformin intolerance, or in combination with hypo-glycaemic agents such as metformin, sulfonyl ureas, and insulin. The present investigation concerns the development and evaluation of effervescent floating tablets of Dapagliflozin which, after oral administration, are designed to prolong the gastric residence time and increase drug bioavailability. A floating drug delivery system (FDDS) was developed using gas-forming agent like sodium bicarbonate and polymers like Pullulan gum, polyethylene oxide and hydroxypropyl methylcellulose (HPMC). The combination of hydrophillic and hydrophobic polymer such as ethyl cellulose was studied. The tablets were prepared by direct compression and evaluated in terms of their physical characteristics, in vitro release, buoyancy, buoyancy lag-time, swelling and erosion index. The formulation was subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominantly diffusion with a minor contribution from polymeric relaxation. DSC and FTIR study of pure Dapagliflozin and formulations showed that there is no drug-polymer interaction. Finally, the tablet formulations found to be economical and may overcome the draw backs associated with the drug during its absorption.**

Index Terms- Dapagliflozin, GRDDS (Gastro Retentive Drug Delivery System), Floating Tablets.

I. INTRODUCTION

From the time of invention of drug administration, oral administration is most often used route for the administration of the most of dosage form for the drug delivery. Various Oral dosage forms has been developing from the last two decades. These dosage forms can be used as the matrix for the drug and can control the release of the drug for a required time and rate.

The International Diabetes Federation (IDF) estimates that in 2024, approximately 589 million adults (ages 20-79) were living with diabetes. This number is projected to rise dramatically, reaching an estimated 853 million by 2050.

So we considered the drug Dapagliflozin which is most emerging in the treatment of diabetes by its efficiency to treat the diabetes[[1]].

Dapagliflozin, is a medication used to treat type 2 diabetes. It is also used to treat adults with heart failure and chronic kidney disease. It inhibits subtype 2 of the sodium-glucose transport proteins (SGLT2), which are responsible for at least 90% of the glucose reabsorption in the kidney. Blocking this transporter mechanism causes blood glucose to be eliminated through the urine[[2]].

Dapagliflozin belong to the Bio-pharmaceutical Classification system Class III it has high solubility but it has low permeability so to enhance the bioavailability we considering GRDDS as suitable dosage form to increase its residence time in the stomach to increase the permeability, whereas stomach is the Absorption site for the Dapagliflozin[[3]].

Dapagliflozin is available in two main dosage strengths: 5 mg and 10 mg tablets. [[4],[5]].

GRDDS stands for Gastro-Retentive Drug Delivery Systems. It's a type of oral drug delivery technology designed to keep a medication in the stomach for a longer period than traditional tablets or capsules. Normally, an oral drug passes through the stomach fairly quickly into the small intestine, where most of the absorption happens. For some drugs, this rapid transit is a problem because of Narrow Absorption Window, Instability in Alkaline pH, Local Action etc.

So to overcome these problems GRDDS are considered as effective dosage from for these drugs[[6],[7]].

GRDDS utilize various clever mechanisms to stay in the stomach, despite its natural emptying process these process include Floating Systems, Swellable/Expandable Systems, Mucoadhesive Systems, High-Density Systems. These processes are utilized to enhance the residence time of the dosage forms and release the drug in the controlled manner[[8]].

Gastro-Retentive Drug Delivery Systems (GRDDS) offer a number of significant advantages over conventional oral dosage forms, addressing some of the key limitations of traditional tablets and capsules. These advantages primarily stem from their ability to keep a drug in the stomach for an extended period, the advantages include Enhanced Bioavailability, Improved Drug Solubility and Stability, Reduced Dosing Frequency and Improved Patient Compliance, Sustained and Uniform Drug Release, Local Drug Delivery to the Stomach, Reduced Drug Wastage[[9]].

While Gastro-Retentive Drug Delivery Systems (GRDDS) offer significant advantages, they also come with a number of disadvantages and limitations that must be carefully considered during development and use. These drawbacks can be related to the drug itself, the formulation, or the patient's physiological state. they may be Unsuitability for Certain Drugs due to its nature of Unstable in Acidic Environment, Limited Acid Solubility, Irritation in the Stomach. Some are due to patient variability which have the difference in Gastric Emptying Time, Stomach Fluid Volume, Migrating Motor Complex (MMC), some formulation challenges and potential for physical side effects will also show significant effect[[10]].

II. MATERIALS AND METHODS

Materials

Dapagliflozin was received from Gift sample from Aurobindo Pharma Ltd, Hyderabad. HPMC K 100M, was received from DOW chemical company, USA, Ethyl Cellulose N 22 was received from ASHA Cellulose Pvt Ltd, Aerosil was received from Sinet chemicals, MCC was Gift sample from Aurobindo Pharma Ltd, Hyderabad, Magnesium Stearate was received from Himedia Pvt LTD, Talc was received from S.D Fine Chemicals Pvt LTD, Hydrochloric acid was received from Merck specialities Pvt LTD, Pullulan gum was received from DOW chemical company, USA, Polyethylene oxide was received from DOW chemical company, USA.

Methods

Dapagliflozin Floating tablets preparation [[11],[12]]

The Floating tablets of Dapagliflozin was prepared by the Direct Compression Process which is general method used for the preparation of the tablets.

Initially Api was weighed as per formulation into mortar and add the binder, polymers, effervescent agent and triturate with the help of the pestle to form the uniformly Api distributed granules, Now add the Lubricant and Glidant to form the free flowing granules.

Now the Granules was introduced into the Tablet compression press which consists of 6mm round punches and compressed to form the Floating Tablets of dapagliflozin.

The Dapagliflozin Floating Tablets was prepared by considering the formulations which was given below:

Ingredients	DAFT-1	DAFT-2	DAFT-3	DAFT-4	DAFT-5	DAFT-6	DAFT-7	DAFT-8	DAFT-9	DAFT-10	DAFT-11	DAFT-12
% Polymer content	60	63	66	40	45	50	23	27	32	63	45	27
Dapagliflozin	10	10	10	10	10	10	10	10	10	10	10	10
Pullulan gum	75	87.5	100	•	•	•	•	•	•	87.5	•	•
PEO Coagulant	.	.	.	50	62.5	75	•	•	•	•	62.5	•
HPMC K 100 M	.	.	.	.	.	.	37.5	47.5	60	•	•	47.5
Ethyl Cellulose N 22	.	.	.	.	.	.	.	.	.	10	7	5
Sodium bicarbonate	35	35	35	35	35	35	35	35	35	35	35	35
Microcrystalline cellulose- PH 200	35	35.5	35	60	60.5	60	72.5	75.5	75	35.5	60.5	75.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Magnesium sterate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	160	173	185	160	173	185	160	173	185	183	180	178

Table 1: Formulations of Dapagliflozin Floating Tablets

Selection of the Solvent for the Dapagliflozin Floating Tablets [[13]]

The Dapagliflozin Floating tablets are controlled release dosage forms which will release the drug Dapagliflozin in the controlled rate in the Stomach which consists of the HCL as the medium.

So 0.1N HCL which refers to the similar gastric fluid in the stomach is referred as the Solvent and the Dissolution medium.

Determination of the λ max of The API (Dapagliflozin) [[14]]

The λ max of the Dapagliflozin was determined by the UV-Vis Spectroscopy with the spectrum program.

Initially 100mg of Dapagliflozin was taken into the 100ml Volumetric and make up to the mark with 0.1N HCL which is labelled as Solution-A with Conc 1000µg/ml.

Now take 1ml from Sol-A into 100ml volumetric flask and make upto the mark with 0.1N HCL which is labelled as Sol-B with Conc 10µg/ml.

Now measure the λ max value of Dapagliflozin in UV-Vis spectroscopy.

The λ max value of Dapagliflozin was observed to be 232nm.

Construction of Calibration Curve of Dapagliflozin [[15],[16]]

The Calibration curve of Dapagliflozin was Constructed in the UV-Vis spectroscopy with the help of the Quantitative program.

Initially 100mg of Dapagliflozin was taken into the 100ml Volumetric and make up to the mark with 0.1N HCL which is labelled as Solution-A with Conc 1000µg/ml.

Now take 10ml from Sol-A into 100ml volumetric flask and make upto the mark with 0.1N HCL which is labelled as Sol-B with Conc 100µg/ml.

Now take 0.5, 1, 1.5, 2 & 2.5 ml from Sol-B into 10ml volumetric flask and make upto the mark with 0.1N HCL of 5, 10, 15, 20 and 25µg/ml.

The Calibration curve of Dapagliflozin was constructed with above prepared dilutions with λ max value of 232nm.

Evaluation of pre-compression parameters of powder [[17],[18]]

The "pre-compression parameters" of a powder for tablet manufacturing refer to the critical characteristics of the powder blend before it undergoes the main compaction process. These parameters are essential for predicting how the powder will behave in a tablet press and for ensuring the final tablet's quality and consistency.

The following pre-compression parameters are considered they are:

The angle of repose

Bulk density & Tapped density

Carr’s index

Hausner’s ratio

Evaluation of post compression parameters of floating tablets of Dapagliflozin

After the compression process, floating tablets are subjected to a series of tests to ensure their quality, safety, and functionality. These "post-compression parameters" are crucial for confirming that the final product meets its design specifications.

The evaluation tests for floating tablets can be broadly categorized into two groups: general tablet properties and specific floating properties.

1. General Tablet Properties[[19],[20],[21]]

   a. Tablet Hardness: It measures the mechanical strength of a tablet and its ability to withstand mechanical stresses during handling, packaging, transportation, and patient use.
   The hardness of tablet was measured by the Monsanto hardness tester.

   b. Tablet Friability: It is used to determine the physical strength of uncoated tablets upon exposure to mechanical shock and attrition with the help of Roche friabilator, which is expressed in terms of percentage. In this, ten tablets were weighed and placed in the friabilator and operated at 25 rpm for about 4 min (100 revolutions). Then, the tablets were dedusted and reweighed. The friability was calculated using the following equation:

$$\text{Friability} = \frac{Initial\ weight - Final\ weight * 100}{Initial\ weight}$$

c. Weight Variation: It is determined by taking 20 tablets randomly from each formulation and weighing them individually using an electronic balance, and the average weight was calculated which was compared with an individual weight of the tablet. The deviation for any two tablets should not exceed more than the average weight.

d. Thickness of tablet: The evaluation of tablet thickness is a crucial quality control test in pharmaceutical manufacturing to ensure consistency and uniformity within a batch. This process is important for ensuring proper dosage, consistent appearance, and efficient packaging.

The thickness was calculated by Vernier caliper.

e. Drug Content Uniformity: Each formulation's five tablets are weighed, then they are ground up in a mortar and combined. The 100ml volumetric flask then received 10mg of the substance. Now from the above solution 10ml of solution is taken into another 1ooml flask and make up to the mark with solvent. The Dapagliflozin concentration in ug/ml was determined by using a standard calibration curve of the drug, Then analyzed spectrophotometrically at 203nm.

2. Specific Floating Properties and In Vitro Evaluation [[22],[23]]

a. Floating Lag Time (FLT): The tablets were dropped into the dissolution medium, which is 0.1NHCL, and the time it took for them to float to the surface of the dissolution media was recorded.

b. Total Floating Time (TFT): The amount of time needed for the tablet to descend to the bottom after it floated to the surface is known as the buoyancy lag time. The entire floating time for floating tablets was measured using the buoyancy lag time test, and the floating behavior was checked. Buoyancy lag time was used to determine the in vitro residence period.

c. In-Vitro Drug Release (Dissolution Study): The prepared dosage form of Dapagliflozin was evaluated which is Floating Tablet.

The Drug release rate of Dapagliflozin was evaluated with dissolution apparatus by considering the following parameters:

Apparatus Type	:USP Type II (paddle)
Buffer	:0.1N HCL
Volume of Buffer	:900ml
R.P.M	:50
Temperature	:37.5+/-0.5°c
Stirrer depth	:25mm
Sampling time	:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 & 12 Hr.

The samples are collected in the test tubes in the mentioned time intervals and measured the absorbance with UV-Vis spectroscopy with λ max value of 203nm and calculated the Concentration of Drug release of samples collected at particular time intervals.

To calculate the release profile, the cumulative percentage of drug release was plotted against time.

III. RESULTS AND DISCUSSION

Determination of the λ max of The API (Dapagliflozin):

The λ max value of Dapagliflozin was observed to be 232nm.

Construction of Calibration Curve of Dapagliflozin: The Calibration curve of Dapagliflozin was constructed with above prepared dilutions with λ max value of 232nm and The Linearity was found to be 0.9991.

pre-compression parameters of Formulation powder:

Table 2: *pre-compression parameters of Formulation powder*

Tests	Bulk Density	Tapped Density	Angle of Repose	Carr's Index	Hausner's Ratio
Daft 1	0.51	0.66	24.00	22.73	1.29
Daft 2	0.50	0.60	31.03	16.67	1.20
Daft 3	0.43	0.61	33.00	30.00	1.43
Daft 4	0.40	0.56	31.94	28.13	1.39
Daft 5	0.36	0.53	36.67	32.35	1.48
Daft 6	0.39	0.50	34.62	21.88	1.28
Daft 7	0.41	0.53	34.14	22.58	1.29
Daft 8	0.40	0.60	33.00	34.38	1.52
Daft 9	0.35	0.56	37.24	37.84	1.61
Daft 10	0.36	0.51	34.41	29.03	1.40
Daft 11	0.38	0.56	30.00	31.25	1.45
Daft 12	0.37	0.56	37.74	34.29	1.52

The formulations showed moderate flowable flow property and compressibility index. Angle of repose ranged from 24.00 to 37.74, Hausner ratio ranged from 1.2 to 1.52 and the compressibility index ranged from 16.67 to 37.84. The BD and TD of the prepared granules ranged from 0.33 to 0.51 and 0.43 to 0.66 respectively.

The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the flow property.

Post compression parameters of floating tablets of Dapagliflozin:

The shape of the tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks. The thickness and diameter of tablets was measured by vernier calipers and was ranged between 3.35 to 5.3 mm.

The hardness of the tablets was measured by Monsanto tester and was in between 4.6–6.3 kg/cm^2.

The friability was measured by Friabilator and was found to be 0.106 to 0.954%, which is an indication of satisfactory mechanical resistance of the tablets.

The drug content estimations showed values in the range of 92.68 to 102.2% which reflects good uniformity in drug content among different formulations.

All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±5% of the weight.

In vitro buoyancy studies

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid).

Formulations	DAFT-1	DAFT-2	DAFT-3	DAFT-4	DAFT-5	DAFT-6	DAFT-7	DAFT-8	DAFT-9	DAFT-10	DAFT-11	DAFT-12
Weight variation (mg)	161±5	172±6	186±6	159±4	170±4	187±6	162±6	172±4	184±5	185±5	181±4	179±7
Tablet Hardness kg/cm^2	4.6±0.2	5.1±0.3	6.3±0.6	4.7±0.1	5.3±0.2	6.2 ±0.5	4.9±0.5	5.3±0.5	6.3±0.5	5.9±0.5	6.1±0.5	5.7±0.5
Tablet diameter (mm)	8	8	8	8	8	8	8	8	8	8	8	8
Thickness (mm)	3.35±0.2	4.12±0.4	5.21±0.2	3.37±0.5	4.22±0.3	5.18±0.5	3.36±0.2	4.18±0.3	5.23±0.5	5.1±0.4	4.9±0.4	5.3±0.5
Friability (%)	0.26±0.1	0.23±0.07	0.48±0.05	0.76±0.2	0.89±0.08	0.77±0.03	0.41±0.09	0.29±0.01	0.38±0.03	0.23±0.04	0.89±0.1	0.29±0.34
Drug Content (%)	97.32±2.3	95.9± 1.5	98.21±1.8	99.75±2.3	98.25±1.8	99.48±2.8	97.35±1.7	96.55±2.4	94.48±1.8	95.9± 1.5	96.25±1.8	96.55±2.4
In vitro buoyancy	>10sec	>13sec	>15sec	>10sec	>15sec	>18 sec	>15 sec	>19 sec	> 22sec	>15sec	>15sec	>19sec
Total Floating time (hr.min)	3.2	5.5	8.3	4.1	6.2	9	4.3	6.4	9.3	>12	>12	>12

Table 3: Post compression parameters of floating tablets of Dapagliflozin

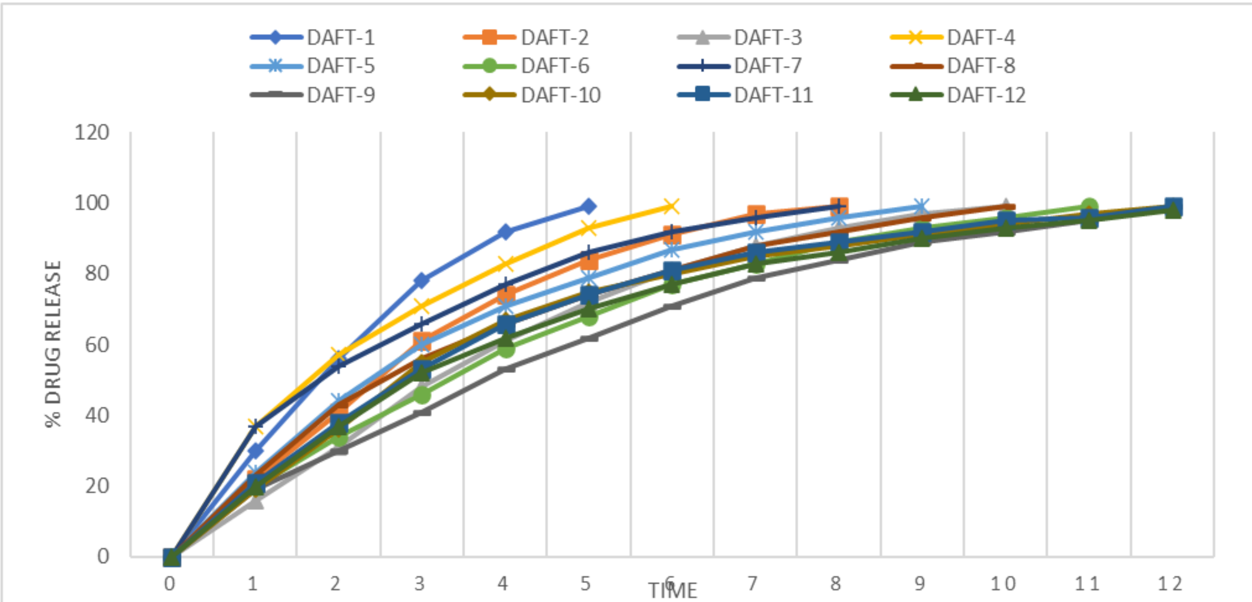
Effect of different polymers over drug release

Tablets were prepared using direct compression with excipients including pullulan gum, PEO coagulant, HPMC K100M, and ethyl cellulose, along with sodium bicarbonate as a gas-forming agent and microcrystalline cellulose for compressibility.

The observation state that tablet using HPMC K 100M is more rate controlling than pullulan gum, PEO coagulant.

Effect of combination of polymers over drug release

The formulations Daft 9-12 are the formulation prepared with combination of Ethyl Cellulose N 22 and Pullalan gum, PEO Coagulant, HPMC K 100 M respectively. Where we can observe the combination of the polymers will enhancing the controlled release rate of the drug than the Formulations Daft 1-8, where single polymer is used in the Formulation was observed in the following graph.



Time (hr)	DAFT-1	DAFT-2	DAFT-3	DAFT-4	DAFT-5	DAFT-6	DAFT-7	DAFT-8	DAFT-9	DAFT-10	DAFT-11	DAFT-12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	30	22	16	37	24	20	37	23	19	19	21	20
2	56	41	31	57	44	34	54	43	30	36	38	37
3	78	61	48	71	60	46	66	56	41	55	53	52
4	92	74	61	83	71	59	77	66	53	67	66	62
5	99	84	72	93	79	68	86	74	62	75	74	70
6		91	81	99	87	77	92	81	71	80	81	77
7		97	88		92	83	96	88	79	85	86	83
8		99	93		96	89	99	92	84	88	89	86
9			97		99	93		96	89	91	92	90
10			99			96		99	92	94	95	93
11						99			95	97	96	95
12									99	99	99	98

Figure 1: Dissolution parameters of Prepared Dapagliflozin floating tablets

Drug-Polymer interaction by FT-IR & DSC:

Composition	Observance
Dapagliflozin	Crystalline, melts at 80.47°C
Dapagliflozin-Pullulan gum + Ethyl cellulose	Shows partial complexation. Some original drug remains with melting point of 81.15°C , but a new, more stable complex is formed that melts at 179.99°C
Dapagliflozin-PEO + Ethylcellulose	Shows partial complexation. Some original drug remains with melting point of 82.23°C, but a new, more stable complex is formed that melts at 168.14°C

Dapagliflozin-HPMC K 100 M+ Ethyl cellulose	Shows partial complexation. Some original drug remains with melting point of 105.22°C, but a new, more stable complex is formed that melts at 183.95°C

Table 4: DSC Data interpretation of combination of polymers with Dapagliflozin

Formulation	Key O-H Peak (cm−1)	Characteristic Excipient Peaks (cm−1)	Interaction Assessment
Dapagliflozin API (Pure Drug)	3383.44	1621.78 (C=C aromatic), 779.47 (C-Cl)	Baseline: Confirms Dapagliflozin structure.
Dapagliflozin-Pullulan gum + Ethyl cellulose	3389.66 (Slight shift/Broadening)	∼1640 (C=C/Other), ∼1034 (C-O-C ether)	Compatible. Weak physical hydrogen bonding (H-bonding).
Dapagliflozin-PEO + Ethylcellulose	3436.87 (Broadening/Shift)	1721.32 (C=O of PEO)	Compatible. Extensive physical H-bonding due to polymer and starch O-H groups.
Dapagliflozin-HPMC K 100 M+ Ethyl cellulose	3428.78 (Broadening/Shift)	1714.34 (C=O of HPMC)	Compatible. Strong physical H-bonding between drug, HPMC, and Starch.

Table 5:FTIR Data interpretation of combination of polymers with Dapagliflozin

Kinetic Data of Dapagliflozin Floating tablets

Kinetics	DAFT 1	DAFT 2	DAFT 3	DAFT 4	DAFT 5	DAFT 6	DAFT 7	DAFT 8	DAFT 9	DAFT 10	DAFT 11	DAFT 12
Zero order (r2)	0.9521	0.9409	0.9346	0.9638	0.9191	0.9423	0.9381	0.9292	0.9504	0.8603	0.8707	0.8977
First order(r2)	0.9143	0.9243	0.9328	0.9671	0.9788	0.9729	0.9761	0.9719	0.9799	0.9827	0.9972	0.9954
Higuchi(r2)	0.9815	0.9761	0.9841	0.9946	0.9769	0.9892	0.9851	0.9839	0.9911	0.9457	0.9534	0.9596
Peppas(n)	1.4991	1.3864	1.2571	1.5789	1.4328	1.3325	1.5826	1.4196	1.2916	1.3726	1.3981	1.5367

Table 6: kinetic data of Dapagliflozin floating tablets

SUMMARY

The standard calibration curve of Dapagliflozin was established in 0.1N HCl showing absorbance maxima at 232 nm with linearity (R^2 = 0.9991) over 5–25 µg/ml concentration range.

Tablets were prepared using direct compression with excipients including pullulan gum, PEO coagulant, HPMC K100M, and ethyl cellulose, along with sodium bicarbonate as a gas-forming agent and microcrystalline cellulose for compressibility.

All formulations displayed good physicochemical properties, with uniform weight variation, hardness (4.6–6.3 kg/cm²), friability below 1%, and rapid onset of buoyancy (< 20 seconds).

Floating and drug release studies in simulated gastric fluid (0.1 N HCl) demonstrated that formulations floated for 3–12 hours depending on polymer content. Pullulan gum-based tablets extended drug release up to 10 hours following zero-order kinetics, whereas PEO and HPMC-based systems followed first-order kinetics.

All showed strong Higuchi correlations ($r^2 > 0.97$), confirming diffusion-controlled release, and Peppas 'n' > 1 values indicated "super Case II" transport, governed by both diffusion and polymer relaxation.

The ethyl cellulose–composited formulations (F10–F12) offered the most prolonged floating (beyond 12 hours) and sustained release up to 12 hours, following first-order release with r^2 = 0.9827–0.9972. These results identified the combination systems as optimal for achieving gastric retention and extended release.

Further in vitro buoyancy images showed consistent floating behavior through 12 hours.

DSC thermograms exhibited sharp endothermic peaks (~80.5–105.2 °C) for both pure drug and polymer blends, confirming the absence of drug–polymer chemical interaction.

FTIR analysis supported this, showing characteristic Dapagliflozin peaks (3367 cm⁻¹ for OH stretch, 1613 cm⁻¹ for aromatic C=C, and 1246 cm⁻¹ for C–O stretch) with no shift or disappearance after formulation, therefore verifying compatibility of excipients with the drug.

Overall, the results confirmed that combining ethyl cellulose with pullulan gum, PEO, or HPMC effectively enhanced the floating duration and controlled the release of Dapagliflozin, making such polymer composites promising candidates for gastro-retentive controlled-release formulations.

CONCLUSION

The study concludes that the Dapagliflozin floating matrix tablets formulated with combinations of ethyl cellulose and polymers such as pullulan gum, PEO, and HPMC successfully achieved prolonged gastric retention and controlled drug release up to 12 hours. The tablets demonstrated immediate buoyancy and sustained release following diffusion and polymer relaxation mechanisms, with no drug-polymer incompatibility observed. These results highlight the potential of ethyl cellulose-polymer composites for effective gastro-retentive drug delivery systems, improving bioavailability and therapeutic efficacy of Dapagliflozin through extended, controlled release in the stomach environment.

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