Formulation and Evaluation of Fast Dissolving Tablet of Dapagliflozin

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Abstract- **The present research work envisages the applicability of superdisintegrants such as crospovidone and croscarmellose sodium in the design and development of fast dissolving formulation of Dapagliflozin by manual experiments. In the present work solubility of drug was enhanced by using inclusion complex. The inclusion complex of drug: β-cyclodextrin was prepared in different ratios by physical mixture method. The direct compression method was used to formulate and evaluate fast dissolving tablet of dapagliflozin. The prepared formulations were evaluated for precompression and post-compression studies. The increased concentration of the superdisintegrants enhanced the porosity of the tablet, due to which it reduced the disintegration time and wetting time and maximum drug release in 30 minutes. From all the results it is concluded that formulation FD6 containing crospovidone was found to be the best formulation in terms of flow property, disintegration time, wetting time, drug content and maximum percentage drug release. It was observed that formulation FD6 shown rapid disintegration time (30.5 sec), wetting time (30.1 sec) and percentage cumulative drug release 98.8% within 30 minutes.**

Keyword: **Dapagliflozin, fast dissolving tablets, bioavailability, glycaemic, superdisintegrants**

I. INTRODUCTION

Dapagliflozin is a highly potent, selective, competitive inhibitor of sodium glucose co- transporter-2 (SGLT2), improves glycaemic control in patients with Type 2 diabetes (T2DM) by reducing renal glucose re-absorption[1,2]. Dapagliflozin belongs to BCS class III drug, and have a bad metallic taste[3]. Since, the solubility of dapagliflozin is low (approx 0.106mg/ml) in aqueous phase hence inclusion complex will be formed to enhance the solubility[4,5]. The formulation of dapagliflozin fast dissolving tablet will enhance the absorption and bioavailability will get fasten and hence the drug will show rapid onset of action[6,7].

The fast dissolving tablets of dapagliflozin were prepared employing crospovidone, croscarmellose sodium in different concentrations as a superdisintegrants by Direct Compression technique. The formulation will enhance the absorption as well as the bioavailability of the drug leading to rapid onset of action[8].

The main aim of current research is to formulate and evaluate fast dissolving tablet of dapagliflozin using crospovidone, croscarmellose sodium as superdisintegrant to produce dosage form having rapid onset of action.

II. EXPERIMENTAL WORK

Dapagliflozin was purchased from Novartis Pharmaceuticals, Hyderabad. Crospovidone and Croscarmellose Sodium were purchased from Yarrow Chem Products Ltd. and Microcrystalline Cellulose, Mannitol, Magnesium Stearate, Talc, from Lobachem Pvt. Ltd. All reagents were used belongs to L. R. grade.

Preformulation Studies:

Determination of wavelength using UV-visible spectroscopy: 10 mg of dapagliflozin was weighed and dissolved into 10 ml of methanol to prepare a 1000 µg/ml stock solution from which a 10 µg/ml dilution was prepared. Baseline correction was performed using methanol and sample was scanned between 200-400 nm and wavelength of maximum absorbance (λ max) was determined[9].

Calibration curve of dapagliflozin in phosphate buffer pH6.8: From Stock B solution the appropriate aliquot of 0.5ml, 1.0ml, 1.5ml, 2.0ml, and 2.5ml were pipetted into different 10 ml volumetric flask and diluted up to 10ml with phosphate buffer pH 6.8 to get different concentration range 5-25µg/ml. The absorbance of each dilution was noted.

Determination of solubility of Dapagliflozin in various mediums: The solubility of dapagliflozin in various medium was determined by shake flask method. In this method 5 ml of each solvent was taken into a vial and an excess amount of dapagliflozin was added. The vials were sealed properly and stirred continuously at 37° ± 2 °C. After solubilization of dapagliflozin, an extra amount of dapagliflozin drug was added to the vials containing drug-solvent mixture and stirred for a period of 6 hours (saturation time). The process was repeated until saturation

solubility of dapagliflozin, indicated by presence of undissolved drug. The mixtures were then kept at room temperaturefor24hrsandthesolutionwasfilteredthroughwhatman‟sfilterpaper.Then diluted with respective solvents i.e. Methanol, phosphate buffer pH 6.8, pH 1.2 HCl buffer and distilled water. The drug concentration was analyzed spectrophotometrically at 221.3 nm using UV-visible spectrophotometer (Shimadzu-1800)[10].

Drug-excipient interaction study: The compatibility of the drug was assessed by drug-excipient interaction study. The drug was mixed with various excipients in a 1:1 ratio in glass vials which were properly sealed & labeled and kept undisturbed at 50°C temperature and 75% RH for 15 days. Physical and chemical observations of all the mixtures were done on initial day and 15th day by TLC.

Thin layer chromatography: Stationary phase was Pre coated silica gel-G, Mobile phase was Toluene: methanol, 7:3v/v. The iodine chamber was prepared and TLC plate was placed in a chamber. Thereafter the plate was removed from chamber and spot was observed.

Selection of excipients:

Table No. 1: Details of excipients

S. No.	Excipients	Purpose
1	Beta-cyclodextrin	Solubility enhancer
2	Crospovidone	Superdisintegrant
3	Croscarmellose Sodium	Superdisintegrant
4	Microcrystalline Cellulose	Disintegrant
5	Mannitol	Diluent
6	Aspartame	Sweetening agent
7	Magnesium Stearate	Lubricant
8	Talc	Glidant

Formulation of fast dissolving tablet:

Experimental design: The manual experiments were performed for the formulation of fast dissolving tablet of Dapagliflozin and the experimental trials were performed at all 12 formulations, in which the two concentrations (1:1, 1:2) of β-cyclodextrin and the three concentrations of two superdisintegrants (crospovidone and croscarmellose sodium) which were varied from lower to higher concentrations[11].

Table No. 2: Composition of Fast Dissolving Tablet

Ingredients	FD 1 mg	FD 2 mg	FD 3 mg	FD 4 mg	FD 5 mg	FD 6 mg	FD 7 mg	FD 8 mg	FD 9 mg	FD 10 mg	FD 11 mg	FD 12 mg
Drug Dapagliflozin	10	10	10	10	10	10	10	10	10	10	10	10
β- cyclodextrin	10	10	10	20	20	20	10	10	10	20	20	20
Crospo vidone	7.5	10	12.5	7.5	10	12.5	-	-	-	-	-	-
Croscar mellose sodium	-	-	-	-	-	-	7.5	10	12.5	7.5	10	12.5
Microcrystalline cellulose	130	130	130	130	130	130	130	130	130	130	130	130
Mannitol	40	40	40	40	40	40	40	40	40	40	40	40
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	4	4	4	4	4	4	4	4	4	4	4	4
Talc	6	6	6	6	6	6	6	6	6	6	6	6

Preparation of inclusion complex by physical mixture method: The solid complexes of dapagliflozin and β-cyclodextrin were prepared in 1:1 and 1:2 molar ratios by physical mixture method. The required quantities of dapagliflozin and β- cyclodextrin were accurately weighed. β-CD (10 and 20mg) was taken separately in two different pestle-mortar. Subsequently, drug (10mg) was slowly incorporated into both pestle-mortars one by one, with continuous trituration for about one hour and passed through sieve no. # 60.

Preparation of fast dissolving tablet by direct compression: Fast dissolving tablets of Dapagliflozin were prepared by direct compression method. All the ingredients were weighed accurately according to the Table no.6.4. All the ingredients were mixed step by step with drug: β-cyclodextrin inclusion complex and triturated continuously for 15 minute. Subsequently talc and magnesium stearate mixed at last & again mixed. Then passed through sieve no. #60.

The powder was compressed using multi-station tablet punching machine (Aidmach Pvt. Ltd.) with 8mm flat punch, B-tooling and corresponding dies.

Evaluation parameter:

Precompression Parameters of powder: Bulk Density, Tapped Density, Carr's index, Angle of repose and Hausner's ratio were performed.

Evaluation of Inclusion complex:

Solubility Determination: An excess amount of prepared Dapagliflozin: β-cyclodextrin inclusion complex at different concentration (1:1, 1:2) were separately dissolved in 5 ml phosphate buffer pH 6.8 in vials and sealed properly and stirred continuously at 37º ± 2 ºC. The process was repeated until saturation solubility of inclusion complex. The solution was kept for 24 hours at room temperature. The solution was filtered and adequately diluted with phosphate buffer pH 6.8. Then solution was analyzed using UV-visible spectrophotometer at 221.3nm.(72)

Post Compression parameter of fast dissolving tablet: Weight variation, Hardness, Thickness, Friability, In-vitro disintegration time, Drug content, Wetting time & Water absorption ratio and In-vitro drug release study were performed.

RESULT AND DISCUSSION:

Preformulation study: Determination of wavelength using UV spectroscopy: The maximum wavelength of Dapagliflozin was found to be 221.3nm.

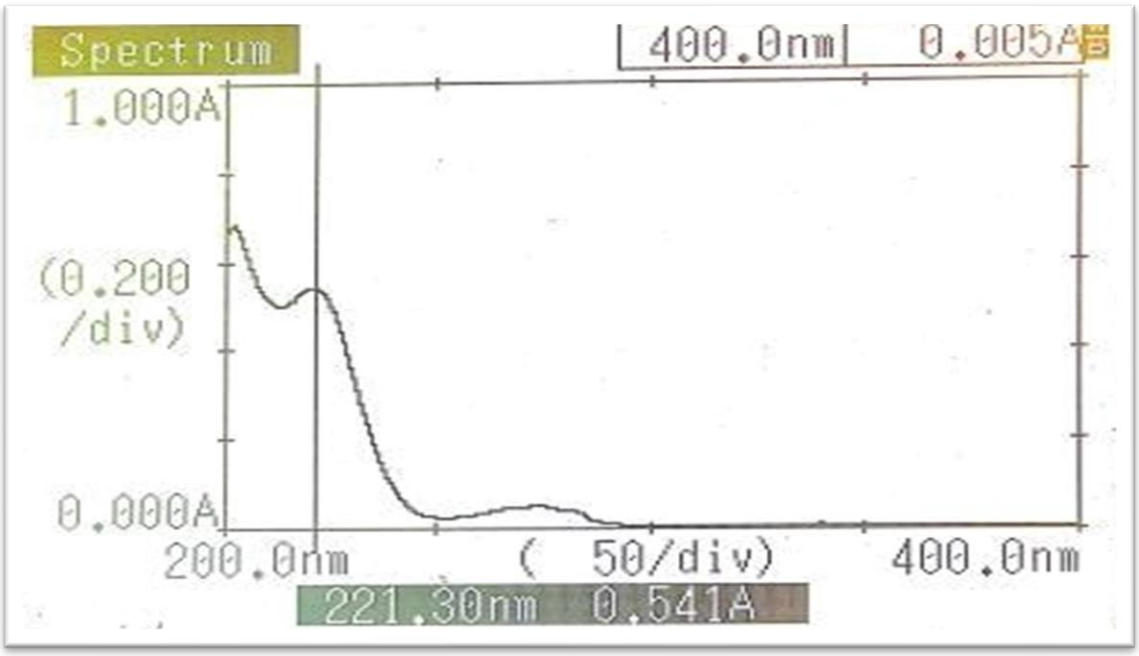

Figure 1: UV Spectrum of Dapagliflozin

Calibration curve of Dapagliflozin in phosphate buffer pH6.8: The calibration curves of dapagliflozin in phosphate buffer pH 6.8 were prepared and shown below:

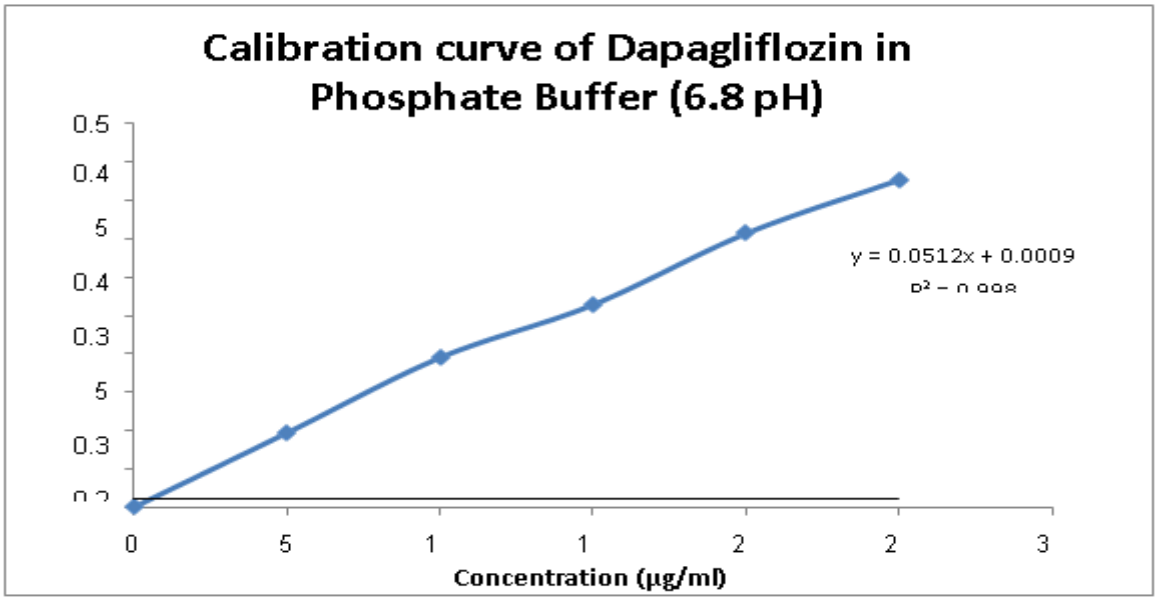

Figure 2: Calibration graph of Dapagliflozin in phosphate buffer pH 6.8 at 221.3nm

Determination of solubility of Dapagliflozin in various medium:
The solubility of Dapagliflozin in various mediums was studied and the results of study were shown in below table:

Table No.3: Solubility data of Dapagliflozin in different mediums

S. No.	Solvent	Solubility (mg/ml) Mean ± SD
1	Methanol	46.318 ± 0.869
2	Phosphate buffer pH 6.8	0.394 ± 0.002
3	pH 1.2 HCl buffer	0.305 ± 0.017
4	Distilled water	0.106 ± 0.002

Determination of solubility of inclusion complex:
The solubility of inclusion complex in phosphate buffer pH 6.8 was studied and the results of study were shown in below table:

Table No. 4: Solubility data of inclusion complex

S. No.	Drug/β-CD Complex	Solubility (mg/ml) Mean ± SD
1	Pure drug	0.394 ± 0.002
2	Drug:β-CD (1:1)	8.361 ± 0.007
3	Drug:β-CD (1:2)	11.525 ± 0.006

Drug-excipient interaction study: The drug (Dapagliflozin) was found to be compatible with various excipients which were selected for formulation of fast dissolving tablet. The compatibility was assessed by TLC and the retention factors of all ratios found similar.

Table No. 5: Data of drug-excipient interaction study

Drug/ drug + Excipient Ratio (1:1)	Physical appearance (initial)	Present Day (Rf)	Physical appearance (final)	After15 Days(R_f)	Inference
Drug (Dapagliflozin)	White	0.54	White	0.54	No Change
Pure Drug + β-cyclodextrin	White	0.51	White	0.52	No Change
Pure Drug + Crospovidone	White	0.52	White	0.53	No Change
Pure Drug + Croscarmellose Sodium	White	0.55	White	0.56	No Change
Pure Drug + MCC	White	0.53	White	0.54	No Change
Pure Drug + Mannitol	White	0.49	White	0.50	No Change
Pure Drug+	White	0.56	White	0.56	No

Aspartame					Change
Pure Drug + Magnesium stearate	White	0.57	White	0.58	No Change
Pure Drug + Talc	White	0.54	White	0.53	No Change
Pure drug + Mixture	White	0.53	White	0.55	No Change

Evaluation of fast dissolving tablet:

Precompression parameters evaluation of powder: The bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose of selected formulations were performed and shown in table No.7.8. The results show that the all formulations that possess a good flow property.

Table No. 6: Evaluation of Precompression Parameters of powder

Formulation Code	Bulk density (gm/ml) (Mean±SD)	Tapped density (gm/ml) (Mean±SD)	Carr's index (%) (Mean±SD)	Hausner's ratio (Mean±SD)	Angle of repose (θ) (Mean±SD)
FD1	0.278±0.001	0.322±0.001	13.544±0.882	1.15±0.010	30.18±0.759
FD2	0.302±0.004	0.353±0.003	14.513±0.972	1.16±0.015	29.21±0.298
FD3	0.321±0.003	0.366±0.003	11.845±0.634	1.13±0.005	28.45±0.796
FD4	0.327±0.003	0.383±0.003	14.692±1.112	1.16±0.015	27.88±0.904
FD5	0.344±0.002	0.389±0.003	11.642±0.185	1.12±0.005	26.74±0.767
FD6	0.356±0.004	0.405±0.004	12.243±0.275	1.13±0.005	25.81±0.260
FD7	0.272±0.003	0.314±0.002	13.252±1.062	1.14±0.015	31.22±0.498
FD8	0.285±0.002	0.337±0.002	15.590±1.376	1.18±0.020	29.47±0.726
FD9	0.304±0.002	0.352±0.003	13.616±1.465	1.15±0.020	29.56±0.647
FD10	0.315±0.002	0.376±0.003	16.370±0.359	1.19±0.005	28.89±0.847
FD11	0.334±0.004	0.396±0.003	15.643±0.677	1.18±0.011	28.91±0.481
FD12	0.355±0.003	0.414±0.003	14.389±0.293	1.16±0.005	26.86±0.678

Evaluation of post-compression parameters of fast dissolving tablet:

The fast dissolving tablet of Dapagliflozin were evaluated like weight variation, hardness, thickness, friability, disintegration time, drug content, wetting time and water absorption ratio. Results of studies were shown in table:

Table No. 7: Weight variation, Hardness, Thickness, and Friability of Formulation FD1-FD12

Formulation Code	Weight Variation (mg) (Mean ±SD)	Thickness (mm) (Mean ± SD)	Hardness(Kg/cm2) (Mean ± SD)	Friability (%) (Mean ± SD)
FD1	217.1±1.351	3.58±0.095	2.5±0.115	0.445±0.015
FD2	219.8±3.305	3.63±0.037	2.6±0.152	0.292±0.017
FD3	222.2±4.416	3.67±0.028	2.6±0.057	0.309±0.015
FD4	227.4±2.450	3.70±0.032	2.6±0.1	0.413±0.016
FD5	230.2±1.503	3.71±0.031	2.7±0.057	0.310±0.008
FD6	232.2±1.665	3.78±0.055	2.8±0.057	0.292±0.015
FD7	217.2±2.650	3.61±0.070	2.5±0.057	0.382±0.015
FD8	220.3±1.435	3.64±0.049	2.6±0.1	0.315±0.019
FD9	222.3±3.450	3.69±0.040	2.7±0.115	0.329±0.013
FD10	227.3±4.360	3.74±0.055	2.6±0.152	0.405±0.011
FD11	229.9±1.493	3.73±0.050	2.7±0.152	0.384±0.015
FD12	232.4±1.404	3.75±0.050	2.7±0.057	0.294±0.005

Table No. 8: Disintegration Time, Drug Content, Wetting time & water absorption Ratio of FD1-FD12

Formulation	Disintegration Time (sec)	Drug Content (%) Mean±SD	Wetting time (sec) Mean±SD	Water absorption Ratio (%)
FD1	38.02±0.569	95.69±0.774	33.97±0.437	60.17±0.196
FD2	39.44±0.559	96.48±0.672	36.34±0.646	58.60±1.257
FD3	31.52±0.597	98.49±0.772	41.67±0.308	55.75±1.863
FD4	34.59±0.299	96.65±0.447	44.21±0.259	58.30±1.305

FD5	37.15±0.577	97.58±0.668	32.21±0.219	56.10±0.578
FD6	30.56±0.370	99.37±0.498	30.11±0.696	53.15±0.204
FD7	33.02±1.115	95.17±0.596	45.43±0.591	59.30±0.386
FD8	34.82±0.488	96.51±0.057	35.33±0.249	57.76±0.357
FD9	32.33±0.3	98.33±0.847	34.02±0.488	54.69±0.430
FD10	35.77±0.691	94.43±0.651	32.56±0.14	58.9±1.225
FD11	36.20±0.537	97.53±0.951	35.50±0.186	55.2±0.420
FD12	31.40±0.549	99.06±0.908	38.05±0.091	54.60±1.230

***In-vitro* drug release study of or dispersible tablet:**

The percentage cumulative drug release from formulations FD1 to FD12 was determined. The formulation FD6 showed the highest release (%) within 30 minutes.

Table No. 9: Percentage cumulative drug release data of FD1 to FD6 formulation of fast dissolving tablets using "Crospovidone" as superdisintegrant:

Time (in min)	% Cumulative drug Release (Mean±SD)					
	FD1	FD2	FD3	FD4	FD5	FD6
0	0	0	0	0	0	0
5	21.74 ± 0.489	24.91 ± 1.497	25.20 ± 0.809	22.95 ± 0.537	24.30 ± 0.839	26.54 ± 0.991
10	40.61 ±0.587	41.37 ± 0.566	49.63 ± 1.201	31.34 ± 0.809	34.97 ± 0.567	36.01 ± 0.546
15	51.68 ± 0.609	53.59 ± 0.829	54.03 ± 1.887	41.09 ± 1.417	43.72 ± 0.546	49.94 ± 0.459
20	60.5 ± 0.786	68.45 ± 0.635	72.5 ± 0.695	53.96 ± 0.546	60.8 ± 0.668	63.57 ± 0.587
25	71.4 ± 0.769	79.98 ± 1.56	84.06 ± 0.236	72.36 ± 0.608	76.7 ± 0.739	81.29 ± 1.207
30	85.09 ± 0.954	93.85 ± 0.819	95.23 ± 1.569	80.25 ± 0.776	92.3 ± 0.728	98.84 ± 0.618

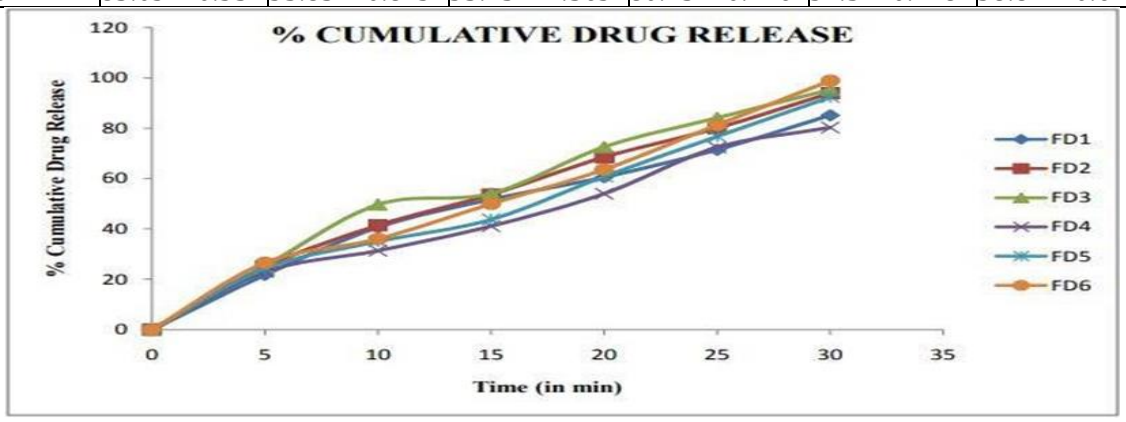

Figure 7.6: Percentage cumulative drug release graph from formulation FD1-FD6

Table No.7.12: Percentage cumulative drug release data of FD7 to FD12 formulation of fast dissolving tablets using "Croscarmellose sodium" as superdisintegrant:

Time (in min)	**% Cumulative drug Release (Mean±SD)**					
	FD7	**FD8**	**FD9**	**FD10**	**FD11**	**FD12**
0	0	0	0	0	0	0
5	19.47 ± 0.207	20.36 ± 0.896	22.74 ± 0.601	21.23 ± 0.926	24.94 ± 0.567	26.41 ± 0.762
10	26.97 ± 0.577	33.77 ± 0.828	34.37 ± 0.579	30.35 ± 0.706	31.74 ± 1.126	35.79 ± 0.697
15	42.79 ± 0.989	48.67 ± 0.667	56.98 ± 1.966	42.58 ± 0.496	49.56 ± 0.556	59.74 ± 0.346
20	66.97 ± 1.112	68.49 ± 0.809	79.36 ± 0.617	59.27 ± 1.463	70.18 ± 0.147	74.20 ± 0.209
25	72.40 ± 2.307	82.39 ± 1.226	86.27 ± 0.563	76.29 ± 0.455	82.01 ± 0.307	89.84 ± 0.465
30	86.5 ± 1.336	90.45 ± 0.129	97.94 ± 0.337	88.05 ± 0.639	96.14 ± 0.559	98.59 ± 0.957

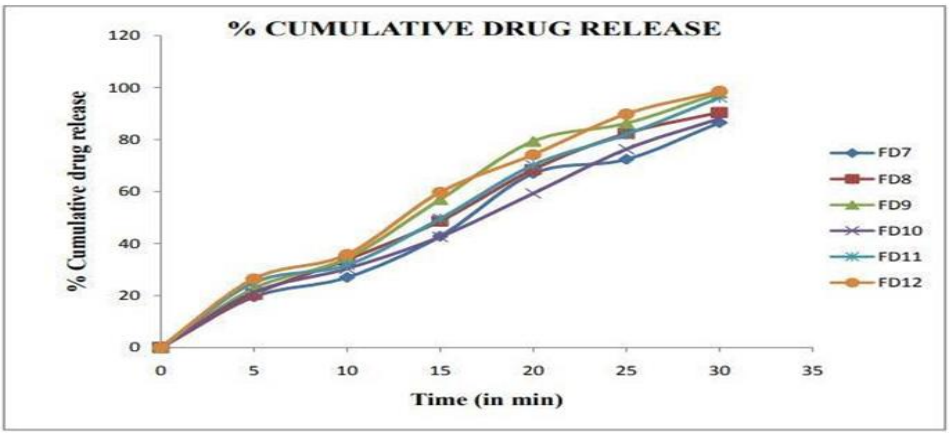

Figure 7.7: Percentage cumulative drug release graph from formulation FD7-FD12

CONCLUSION:

The present research work envisages the applicability of superdisintegrants such as crospovidone and croscarmellose sodium in the design and development of fast dissolving formulation of Dapagliflozin by manual experiments. In the present work solubility of drug was enhanced by using inclusion complex. The inclusion complex of drug: β-cyclodextrin was prepared in different ratios by physical mixture method. The direct compression method was used to formulate and evaluate fast dissolving tablet of dapagliflozin. The formulation prepared were evaluated for precompression studies such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose which were found to be within limits. The increased concentration of the superdisintegrants enhanced the porosity of the tablet, due to which it reduced the disintegration time and wetting time and maximum drug release in 30 minutes.
Compressed tablets were evaluated for post-compression studies like weight variation, hardness, thickness, friability, disintegration, drug content which were found to be good. It was concluded that the addition of drug: β-cyclodextrin inclusion complex leads to improved solubility of drug at optimum concentration (1:2). From all the results it is concluded that formulation FD6 containing crospovidone was found to be the best formulation in terms of flow property, disintegration time, wetting time, drug content and maximum percentage drug release. It was observed that formulation FD6 shown rapid disintegration time (30.5 sec), wetting time (30.1 sec) and percentage cumulative drug release 98.8% within 30 minutes.Thus the present study demonstrated the potential of the formulated fast dissolving tablet for rapid absorption, improved bioavailability, effective therapy and improved patient compliance.

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