IMPACT: International Journal of Research in Applied, Natural and Social Sciences (IMPACT: IJRANSS)
ISSN(P): 2347-4580; ISSN(E): 2321-8851
Vol. 5, Issue 1, Jan 2017, 61-72

EFFECT OF VARIOUS SUPERDISINTEGRANTS ON IMMEDIATE RELEASE FORMULATIONS OF SGLT2 INHIBITOR DAPAGLIFLOZIN

KARUNA PRIYA CHITRA[1], M.CHINA ESWARAIAH[2] & M.V BASAVESWARARAO[3]

[1]Research Scholar, Center for Research Studies, Krishna University, Machilipatnam, Andhra Pradesh, India

[2]Department of Pharmaceutics, Anurag Pharmacy College, Ananthagiri (V), Kodad (M), Nalgonda, Andhra Pradesh, India

[3]Special Officer, Krishna University, DR. MRAR Campus, Nuzvid, Andhra Pradesh, India

ABSTRACT

Type II diabetes is the most common form of diabetes accounting for 90% of diabetes cases. Recently, few novels anti diabetic drugs emerging which belongs to sodium glucose transporter -2 inhibitors (SGLT2). These SGLT2 inhibitors prevent the reabsorption of glucose into blood by the kidney. The present study was under taken to evaluate the effect of various superdisintegrants on immediate release of SGLT2 inhibitor Dapagliflozin containing formulations. In the present study, total 12 formulations were developed various superdisintegrants like Sodium starch glycolate, crosscaremellose sodium, pregelatinized starch and kyron T-314 were used in varying concentration and tablets were prepared by direct compression technique. All the prepared formulations subjected for pre compression and post compression parameters, disintegration time, dispersion, wetting time profiles and *in-vitro* dissolution profiles. Results revealed that formulation containing 6% Kyron T-314 (IR12) was found to be the best amongst all other having 99.93% of drug release in 30 minutes. The optimized formulation IR12 (6% kyron T-314) also showed satisfactory drug content (99.65%), disintegration time of 20 seconds and satisfactory stability.

KEYWORDS: Dapagliflozin, Superdisintegrants, Disintegration Time, Type II Diabetes

INTRODUCTION

Because of the progressive nature of the disease, most patients with type 2 diabetes mellitus eventually require multiple treatments to achieve glycaemic targets. The majority of available therapies are insulin dependent, aiming to decrease insulin resistance and increase insulin secretion. Sodium glucose co-transporter 2 (SGLT2) inhibitor like dapagliflozin, a new class of antidiabetic agents, limit renal glucose reabsorption promoting urinary excretion of glucose, thereby reducing plasma glucose[1]. Most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). Selection of proper Disintegrants and its effect plays a crucial role to release the active medicament of such tablets [2]. Superdisintegrants provide quick disintegration effect when they come in contact with GI fluids due to the combined effect of swelling and water absorption of the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, which promotes the wettability and dispersibility of the system, thus enhancing the disintegration, dissolution and bioavailability [3]? The present study was attempted to prepare immediate release tablets of dapagliflozin: comparative studies of selected superdisintegrants with various concentrations by direct compression technique. Prepared formulations were subjected to pre and post compression studies.

CHARACTERIZATION OF PURE DRUG

Organoleptic Properties

Table 1: Color, Odour and Taste Description of Pure Drugs

Drug Name	Colour	Odour	Taste
Dapagliflozin propanediol	White crystalline powder	None	None

Table 2: Solubility Study of Dapagliflozin

Solvent	Dapagliflozin
Water	Freely soluble
Ethanol	Soluble
DMSO	Freely soluble
DMF	Freely soluble
METHANOL	Soluble
0.1N HCl	Soluble
Acetate buffer pH 4.5	Soluble
Phosphate buffer pH 6.8	Soluble

DSC Study

DSC thermogram was recorded to study the thermal behavior of the drug. DSC thermogram of Dapagliflozin as shown in Figure.1

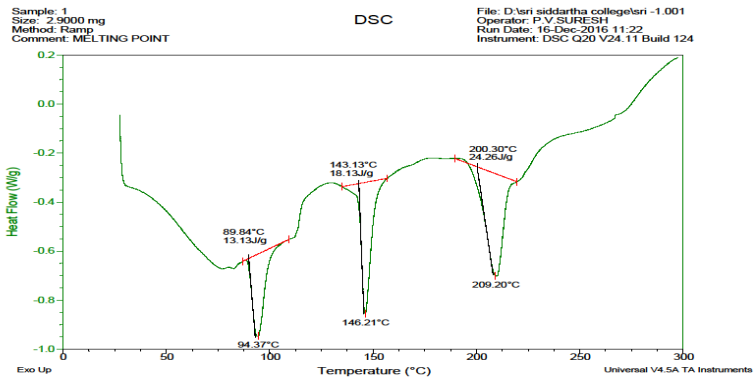

Figure 1: DSC Thermogram of Dapagliflozin (Pure)

FT-IR Study

The IR spectrum of the sample was recorded and the functional groups where interpreted as per the structure and were found to be appropriate or matching the structure of the drug.

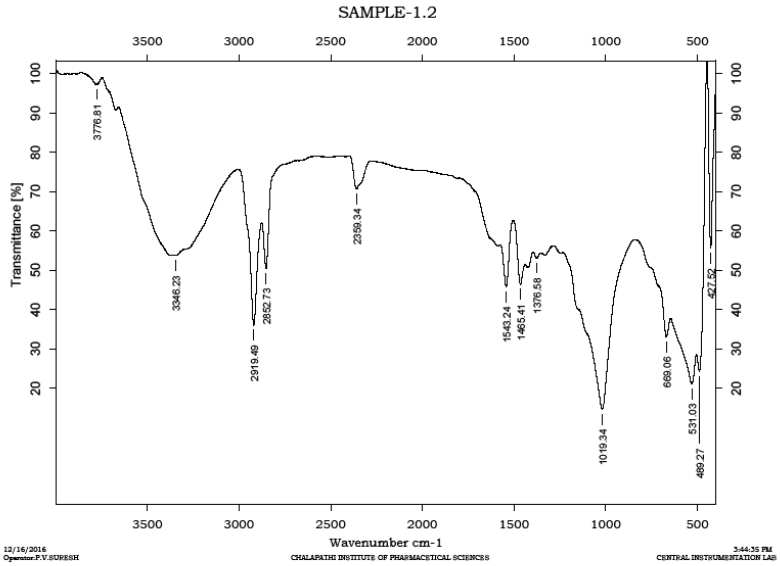

Figure 2: FTIR Spectrum of Dapagliflozin (PURE)

MATERIALS AND METHODOLOGY

Dapagliflogin (Shanghai send pharmaceutical technology co, Ltd, China), lactose (SD fine chem) Micro crystalline cellulose (MCC) PH 102 (Goyal chem) Sodium starch glycolate (SSG) (Amishi Drugs & Chemicals Private ltd), Crosscarmellose sodium (CCS) (Crest cellulose), pregelatinized starch (shreeji pharma), kyron T-314 (Corel Pharma Chem), Iron oxide red(Durga ceramic) and all other chemicals and reagents are of analytical grade.

Drug Excipients Compatability Studies

The drug and excipients compatability studies were conducted inorder to check the formulation is suitable to produce good efficacy and safe therapy. Compatibility studies are carried out by weighing definite proportions of drug and excipient and kept in glass vials, which is stored at 40^{o}C / 75%RH for one month. The drug, polymer and other formulation ingredients were characterized by IR spectroscopy using a FT-IR 8400S the spectra were taken by KBr discs method in the range of 4000–500 cm–1. [4]

Table 3: Drug Excipients Compatability Studies

Ingredients	Ratio	Physical Description (Initial)	Condition (40^{o}c / 75%RH)			
			After One Week	After Two Week	After Three Week	After Four Week
Dapagliflozin + MCC	1:1	White powder	NCC	NCC	NCC	NCC
Dapagliflozin + lactose	1:1	White powder	NCC	NCC	NCC	NCC
Dapagliflozin + Kyron T-314	1:1	White powder	NCC	NCC	NCC	NCC
Dapagliflozin +SSG	1:1	White powder	NCC	NCC	NCC	NCC
Dapagliflozin +CCS	1:1	Cream to off White powder	NCC	NCC	NCC	NCC
Dapagliflozin +Pregelatinised starch	1:1	White to off white powder	NCC	NCC	NCC	NCC
Dapagliflozin +talc	1:1	White powder	NCC	NCC	NCC	NCC
Dapagliflozin +magnesium stearate	1:1	White powder	NCC	NCC	NCC	NCC
Dapagliflozin + iron oxide red	1:1	Brick red colour powder	NCC	NCC	NCC	NCC

NCC-No Colour Change

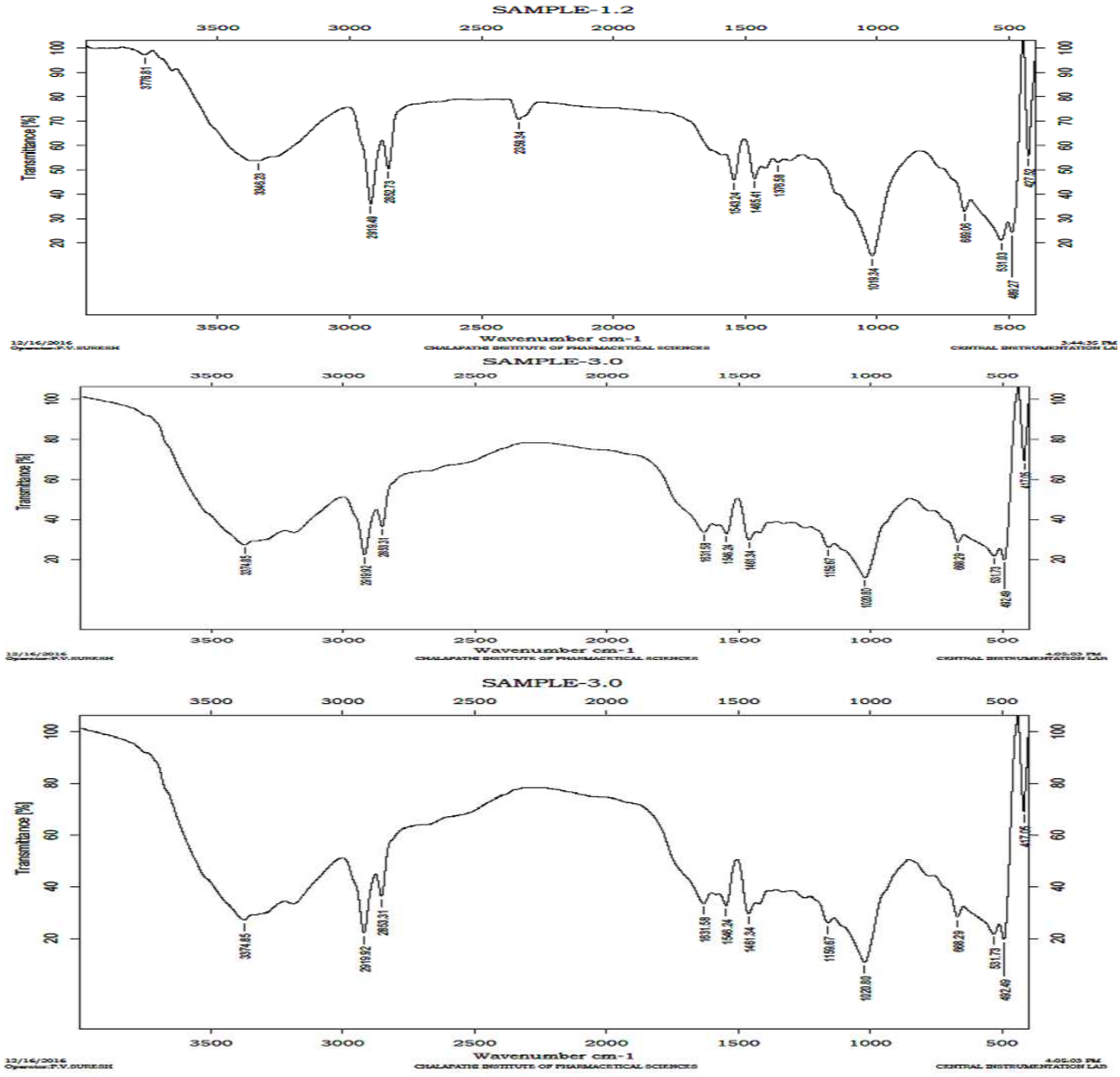

Figure 3: FTIR Spectrum of Dapagliflozin, its Mixture with Other Excipients Before and After Accelerated Stability Studies

PROCEDURE FOR IMMEDIATE RELEASE TABLETS CONTAINING DAPAGLIFLOZIN

Direct Compression Method

Various formulations were prepared using four different super disintegrating agents in different concentrations by direct compression method using MCC as filler. Weigh all the ingredients and passed through sieve #40. Mix all ingredients as per geometric dilution until to get uniform blend except magnesium stearate and talc. Weigh accurately magnesium stearate and talc previously passed through sieve #80 and mix them well with initial blend. The obtained blend was compressed in to tablets on 10 station rotary punching machine.

Table 4: Formulation of Dapagliflog in Immediate Release Tablets

Ingredients (mg)	BATCH NO											
	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9	IR10	IR11	IR12
Dapagliflozin	2.5	2.5	2.5	2.5	2.5	2.5	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	20.0	20.0	20.0	20.0	20.0	20.0
MCC pH 102	118.5	116.5	114.5	120.5	119.5	118.5	116.5	111.5	106.5	119.5	117.5	115.5
SSG	3.0	5.0	7.0	-	-	-	-	-	-	-	-	-
CCS	-	-	-	1.0	2.0	3.0	-	-	-	-	-	-
Pregelatinized starch	-	-	-	-	-	-	5.0	10.0	15.0	-	-	-
Kyron T-314	-	-	-	-	-	-	-	-	-	2.0	4.0	6.0
Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0	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	2.0	2.0	2.0	2.0	2.0	2.0
Total (mg)	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**

EVALUATION [5]

Weight Variation

Twenty tablets were weighed collectively and individually. Average weight was calculated and based on the obtained weights % weight variation was calculated using the formula,

$$\% \text{ Weight Variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100$$

Hardness

Hardness of the tablet was tested by placing the tablet longitudinally in between the two plungers of the Monsanto tablet hardness tester and the obtained hardness was mentioned in terms of kg/sq.cm. Limits for Hardness are 4-6kg/sq.cm.

Friability

The friability of the tablets was determined by Roche Friabilator in which the tablets were subjected to the combined effect of abrasions and shock in a plastic chamber revolving at 25rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of 10 tablets were placed in the friabilator and allowed to rotate for 100 revolutions. Later the tablets were degusted and the tablets were reweighed.

Percent friability is given by the formula;

$$\%F = (1-W/W0) \times 100$$

Where, W0 is the initial weight of tablets before test

W is the final weight of tablets after test

Limits for friability are % friability should not be more than 1%.

Thickness

The thickness of the tablets was determined using a vernier caliper. Tablets from each formulation were used and average values were calculated.

Disintegration Time of Immediate Layer

Single dosage unit was placed in each of the six tubes of the basket and added a disk. Operate the apparatus using water as the immersion fluid, maintained at 37 ± 2^{o}C. Time was noted when disintegration completed for all prepared samples.

Dispersion Time of Immediate Layer

Take ramdomly 6 tablets and place them in to the beaker containing 100ml of water. Stit them gently until they get dispersed, later pass them using a screen with sieve 22# to get a smooth dispersion.

Wetting Time of Immediate Layer

Take petridish and pour the die solution up to 3/4th level. Place the four folded tissue paper on the die solution and put the tablet above the tissue paper then note down the time taken by the tablet to wet completely.

Dissolution Studies for Immediate Layer [6]

In-vitro dissolution tests of all prepared formulations were carried out using USP apparatus type I (ELECROLAB TDT 08 T, Bombay). The dissolution medium consisted of 1000 ml pH 6.8 maintained at 37 ± 0.5^{0}C and stirred at 75 RPM. Samples (10 ml) were withdrawn at predetermined time intervals of 5, 10, 15, 20 and 30 min. Equal amount fresh dissolution medium, maintained at same temperature, was replaced immediately, and withdraw sample was analyzed by HPLC under optimized chromatographic conditions. Percentage drug release was computed from prepared standard curve. The release study was conducted in the triplicate and mean values were plotted.

Chromatographic Conditions

Table 5

Mobile Phase	Acetonitrile: Orthophosphoric Acid (55:45)
Column	BDS
Flow rate	1.0ml/min
Column temperature	Room temperature(20-250 C)
Sample temperature	Room temperature(20-250 C)
Wave length	203nm
Run time	10 min

RESULTS AND DISCUSSIONS

The present study of Dapagliflozin immediate release tablets were developed with a view to deliver the drug immediately. The formulation development work was initiated with direct compression method and a total of 12 formulations (IR1-IR12) were prepared. The formulated tablets were evaluated for various pre compression parameters and post compression parameters like thickness, hardness, weight variation, and friability, and disintegration test, dispersion, wetting time, drug content uniformity and in vitro release studies. The formulation IR12 showed satisfactory physical parameters, and it was found to be stable among other formulations.

Pre-Compression Parameters

Table 6: Flow Property of Prepared Formulations Blend

Batch No	Bulk Density (gm/cm^3)	Tapped Density (gm/cm3)	Angle of Repose (θ)	Carr's Index (%)	Hausners Ratio
IR1	0.57±0.02	0.71±0.02	27.2±1.2	21.2±1.4	1.30±0.2
IR2	0.56±0.01	0.71±0.03	25.3±1.6	24.5±1.6	1.22±0.2
IR3	0.56±0.02	0.69±0.01	26.0±1.3	19.8±1.4	1.25±0.1
IR4	0.57±0.03	0.69±0.02	24.2±1.2	20.3±1.1	1.28±0.2
IR5	0.57±0.02	0.71±0.02	27.2±1.6	21.2±1.6	1.30±0.2
IR6	0.56±0.01	0.71±0.03	26.4±1.6	24.5±1.7	1.22±0.2
IR7	0.56±0.02	0.70±0.01	27.0±1.8	18.6±1.6	1.25±0.2
IR8	0.55±0.03	0.72±0.03	26.5±2.1	17.3±1.8	1.23±0.3
IR9	0.57±0.03	0.69±0.02	27.2±2.0	20.3±1.5	1.28±0.2
IR10	0.53±0.04	0.63±0.01	26.8±1.4	15.8±0.03	1.18±0.03
IR11	0.52±0.01	0.68±0.03	27.3±1.7	23.5±0.03	1.30±0.03
IR12	0.54±0.04	0.67±0.03	26.4±2.1	19.4±0.03	1.24±0.03

All values are expressed as mean ± standard deviation, n=3

All the 12 formulations were evaluated for pharmacotechnical parameters like weight variation, hardness, thickness and friability. Average weight of the tablet did not deviate more than 7.5% which confirmed IP specification. Friability of all the formulations was below 1% which also confirmed specification. In preliminary study, IR1-IR3 batches were SSG (3-7%) was used as super-disintegrating agent. Hardness, friability, disintegration time, dispersion time and wetting time for preliminary batches IR1 to IR3 were found between 4.1-4.2 kg/cm^2, 0.482-0.541%, 29-24 sec, 136-75 sec, 125-80sec respectively. Very less disintegration time obtained in batch IR3 was due to high concentration of super-disintegrating agent (SSG) in formulation. For IR4-IR6 batches where CCS (1-3%) was used as super-disintegrating agent. IR4-IR6 batches where CCS (1-3%) was used as super-disintegrating agent. Hardness, friability, disintegration time, dispersion time and wetting time for preliminary batches IR4 to IR6 were found between 4.0-4.2 kg/cm^2, 0.57-0.63%, 27-31sec, 139-85 sec, 132-88sec respectively. IR4 formulation shows more disintegration time compared to IR5 and IR6 due to presence of less concentration of superdisintegrant. IR7-IR9 batches were pregelatinized starch (5-15%) was used as super-disintegrating agent.

Hardness, friability, disintegration time, dispersion time and wetting time for preliminary batches IR7 to IR9 were found between 4.1-4.2 kg/cm^2, 0.42-0.69%, 25-65 sec, 146-79 sec, 142-96 sec respectively. IR7 formulation shows more disintegration time compared to all other formulations this may be pregelatinized starch alone is not sufficient enough to provide desired disintegrant effect. IR10-IR12 batch where Kyron T-314 (2-6%) was used as super-disintegrating agent. Hardness, disintegration time, wetting time and friability for preliminary batches IR10 to IR12 were found between 4.1-4.2 kg/cm^2, 0.47-0.53%, 20-26 sec, 25-45sec and 28-33 sec respectively. Very less disintegration time obtained in batch IR12 was due to high concentration of super-disintegrating agent (Kyron T-314) in formulation. IR12 batch had given the best results with the disintegration time of 20 sec, friability of 0.47%, hardness of 4.2 kg/cm^2 with 99.65 as drug content.

Post Compression Study Data

Table 7: Post Compression Study Data of Prepared Formulations

Batch No	Average wt (mg) n=20	Thickness(mm) n=10	Hardness (kg/cm2) n=6	Friability(%) n=10
IR1	151.2±2.1	2.56 ± 0.03	4.2± 0.2	0.541
IR2	150.8±1.8	2.55 ± 0.04	4.1± 0.4	0.482
IR3	150.3±1.5	2.56 ± 0.02	4.1± 0.2	0.528
IR4	149.7±1.8	2.52 ± 0.01	4.2± 0.3	0.574
IR5	149.9±1.9	2.52 ± 0.04	4.0± 0.5	0.631
IR6	149.2±1.8	2.58 ± 0.02	4.1± 0.1	0.597
IR7	151.2±2.1	2.59 ± 0.04	4.1± 0.3	0.691
IR8	150.5±1.8	2.52 ± 0.04	4.1± 0.8	0.624
IR9	150.3±1.5	2.58 ± 0.04	4.2± 0.4	0.428
IR10	149.8±1.8	2.52 ± 0.02	4.2± 0.2	0.517
IR11	150.1±1.9	2.51 ± 0.04	4.1± 0.3	0.535
IR12	150.2±1.8	2.53 ± 0.02	4.2± 0.1	0.476

All values are expressed as mean ± standard deviation, n=3

Table 8: Disintegration Time, Dispersion Time, Wetting Time Profiles and Drug Content of Prepared Formulations

Batch No	Disintegration Time (sec)n=6	Dispersion Time (sec) n=6	Wetting Time (sec) n=6	Drug Content (%)
IR1	29±2	136±11	125±9	101.05
IR2	25±2	95±8	97±5	99.47
IR3	24±1	75±6	80±6	98.28
IR4	31±2	139±5	132±8	99.65
IR5	29±1	104±6	101±8	101.05
IR6	27±1	85±7	88±6	99.47
IR7	65±4	146±7	142±6	98.28
IR8	35±3	112±4	123±4	99.12
IR9	25±2	79±3	96±4	100.08
IR10	26±3	45±3	33±3	100.93
IR11	22±3	30±2	30±3	98.34
IR12	20±2	25±2	28±3	99.65

All values are expressed as mean ± standard deviation, n=3

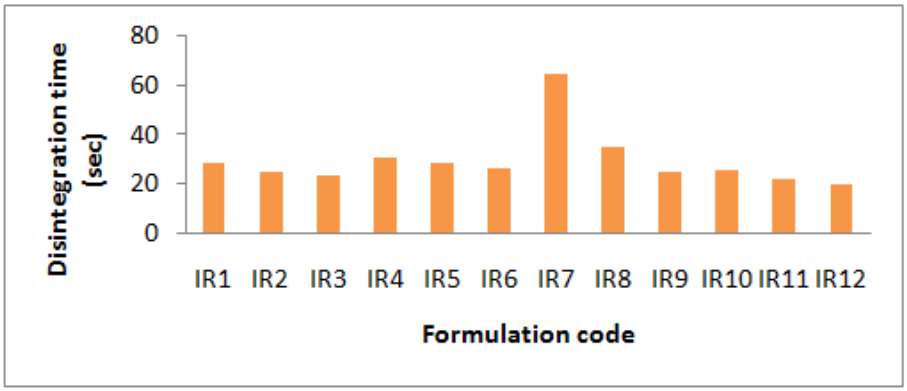

Figure 4: Disintegration Time Profiles of Prepared Formulations

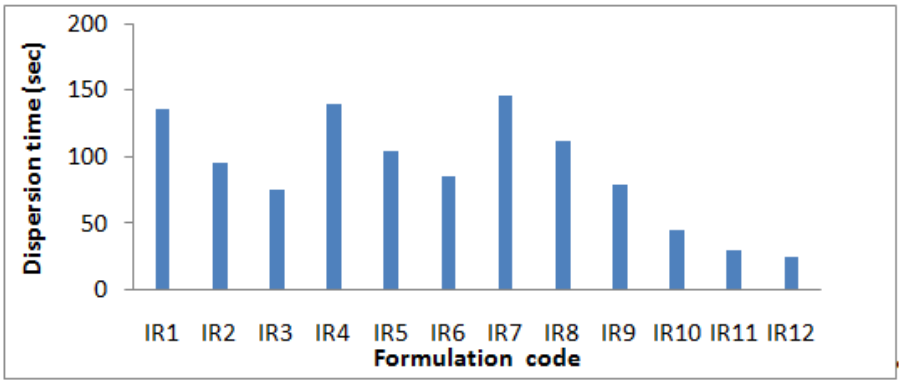

Figure 5: Dispersion Time Profiles of Prepared Formulations

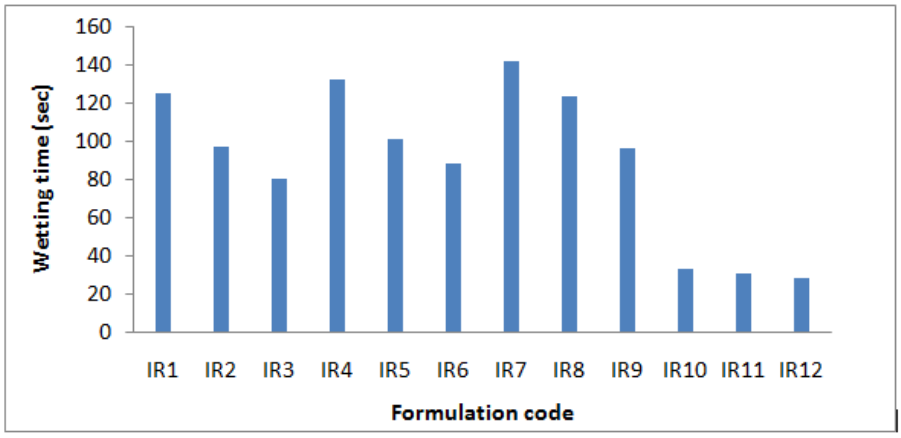

Figure 6: Wetting Time Profiles of Prepared Formulations

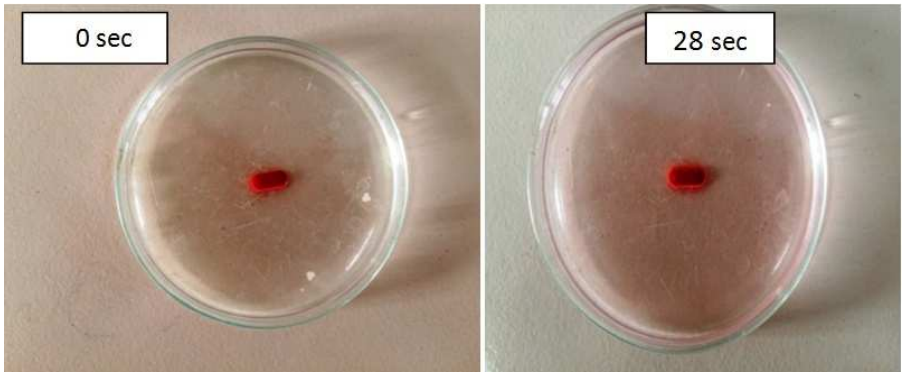

Figure 7: Wetting Times Images of Optimized Formulation IR12

Data shown in table indicated there was no difference in results of weight variation, hardness and friability as well as in assay The hardness of the tablets was found to be in the range of 4.1 to 4.2 kg/cm^2 whereas the percentage friability of all the formulations was found below 1% indicating that the friability was within the prescribed limits. The tablets were found to contain 99.28 to 101.05 % of the labelled amount of Dapagliflozin indicating uniformity of drug content. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all the formulation passed the test for uniformity as per official requirements. From the results of disintegration time, it was found that the tablets of batch IR12 have minimum disintegration time i.e. 20±2 sec. whereas the batch IR7 has maximum disintegration

time 65±4 sec. From the results of dispersion time and wetting time, it was found that the tablets of batch D12 has minimum dispersion and wetting time i.e. 25±2 sec and 28±3 sec. respectively, where as the batch IR7 has maximum dispersion and wetting time 146±7 sec and 142±6 sec. respectively.

Table 9: *In-vitro* Dissolution Profile of Preliminary Trial Formulations

Time (min)	Cumulative % Drug Release											
	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9	IR10	IR11	IR12
5	54.48 ±0.61	59.36 ±0.30	62.77± 0.33	55.65 ±0.51	58.12 ±0.55	59.71 ±0.51	50.24 ±0.11	54.37 ±0.51	56.35 ±0.35	45.87 ±0.53	51.66 ±0.29	59.24± 0.57
10	86.24 ±0.51	89.54 ±0.49	91.2±0 .53	75.3± 0.29	80.l8 ±0.26	82.46 ±0.29	78.54 ±0.29	82.76 ±0.21	84.77 ±0.26	78.82 ±0.46	84.44 ±0.46	91.56± 0.43
15	96.15 ±0.42	98.62 ±0.51	99.35± 0.41	95.56 ±0.34	98.21 ±0.31	98.42 ±0.37	95.67 ±0.35	97.24 ±0.33	97.53 ±0.19	98.85 ±0.36	99.25 ±0.25	97.15± 0.22
20	98.51 ±0.53	98.62 ±0.51	99.35± 0.41	97.98 ±0.22	98.21 ±0.31	98.42 ±0.37	96.67 ±0.45	97.24 ±0.44	97.53 ±0.53	98.85 ±0.22	99.25 ±0.54	98.87± 0.28
30	-	-	-	-	-	-	-	-	-	-	-	99.93± 0.51

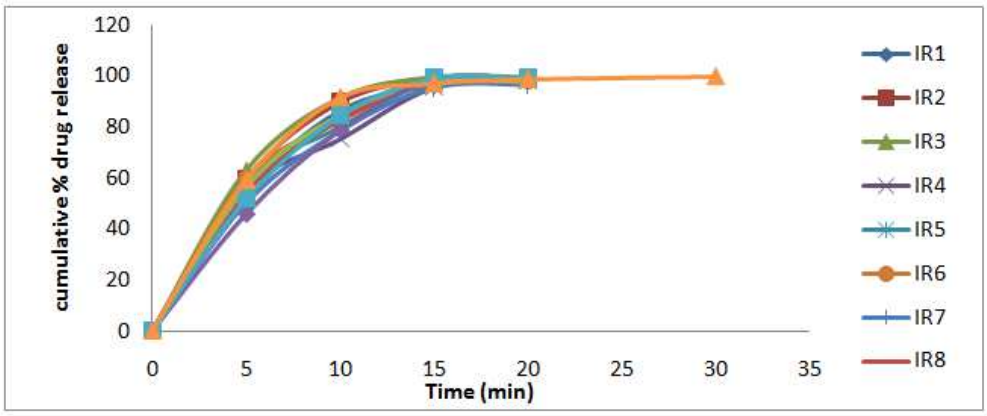

Figure 8: Dissolution Profiles of Prepared Formulations

The *in-vitro* dissolution study was carried out according the prescribed method. The results of drug release studies were shown in table. All the formulations released more than 90% of drug within 10 min. After 10 min of dissolution testing, only batch IR3 and IR12 released more than 90 % of drug all other formulations released the drug within 15 min. Batches composed of SSG and Kryon T-314 in highest concentration indicates good superdisintegranting effect thus the concentration of superdisintegrant and its nature plays an important role to release the drug. For optimization, physical parameters were also considered along with *in-vitro* drug release. After considering all parameters on the basis of considerable disintegration time, good wetting time and the least concentration of disintegrating agent used, batch IR12 containing 6% Kyron T-314 was optimized as immediate layer with 99.93% as drug release in 30 minutes.

CONCLUSIONS

From the present study it can be concluded that the batch IR12 containing 6% Kyron T-314 was found to be the best formulation, amongst 12 batches, with the release rate of 99.93%. Further from this study it can be concluded that, 6% Kyron T-314 can further may used as super disintegrant for optimization of immediate release studies.

REFERENCES

1. Gary Kilov, Stephen Leow,Merlin Thomas SGLT2 inhibition with dapagliflozin,A novel approach for the management of type 2 diabetes, reprinted from australian family physician vol. 42, no. 10, october 2013
2. Mukesh C. Gohel, Rajesh K. Parikh, Bansari K. Brahmbhatt& A. R. Shah. Preparation and Assessment of Novel CoprocessedSuperdisintegrant Consisting of Crospovidone and Sodium Starch Glycolate: A Technical Note. AAPS PharmSciTech. 8 (1) (2007) E1- E6.D.
3. T. Kaur, B. Gill, S. Kumar & G. D. Gupta. Mouth Dissolving Tablets: A Novel Approach to Drug Delivery. International Journal of Current Pharmaceutical Research. Vol 3 (2010) 1-7.
4. Hitesh P. Patel, Preeti Karwa, Rama Bukka, Nitesh J. Patel, formulation and Evaluation of Zolpidem Tartrate immediate release tablets. International Journal of Pharmaceutical Sciences Review and Research, March – April 2011; 7(2): 014, 80-85.
5. Jaimin Modi, Ravindra Kamble, Dr. Chetan Singh Chauhan, Nisarg Patel, Formulation development & optimization of Immediate Release Tablet of Fexofenadine Hydrochloride, Journal of Pharmaceutical Science Bio scientific Research, 2013; 3(2): 5161.
6. Dissolution Testing of Immediate Release Solid Oral Dosage Forms, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), August 1997; 1-12.