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Design and Solubility Enhancement of Empagliflozin Immediate Release Tablets by Using Solid Dispersion Method

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ABSTRACT

To review available studies of Empagliflozin, a sodium glucose co-transporter-2 (SGLT2) inhibitor approved in 2014 by the European Commission and the United States Food and Drug Administration for the treatment of type 2 diabetes mellitus (T2DM). Reference lists from retrieved articles were searched manually for additional peer-reviewed publications. Study Selection and Data Extraction: All publications reporting clinical trials of Empagliflozin were eligible for inclusion. Data Synthesis: Empagliflozin is a new once-daily oral SGLT2 inhibitor with a mechanism of action that is independent of β-cell function and the insulin pathway. Data from a comprehensive phase III clinical trial program have demonstrated its efficacy as monotherapy, as add-on to other glucose-lowering agents, and in different patient populations. In these studies, empagliflozin resulted in improvements in blood glucose levels as well as reductions in body weight and blood pressure. Preparation of Empagliflozin solid dispersion of empagliflozin in PEG-6000 and Plasdone-S630 are prepared in the ratio (1:4) by using solvent evaporation method.

INTRODUCTION

Empagliflozin is an orally administered selective sodium glucose cotransporter2 (SGLT2) inhibitor which lowers blood glucose in people with type 2 diabetics by blocking the reabsorption of glucose in kidneys and promoting the excretion of excess glucose in urine. The sodium glucose cotransporter2 (SGLT2) located in the proximal tubule of the nephron is estimated to facilitate 90% of this reabsorption as a potent and selective competitive inhibitor of the SGLT2 protein. Sodium glucose co-transporters inhibitors offer an insulin independent mechanism for improving blood glucose levels. Since they promote urinary glucose excretion by inhibiting glucose reabsorption in the kidney. In addition to glucose control, SGLT2 inhibitors are associated with weight loss and blood pressure reductions and do not increase the risk of hypoglycaemia.

The main objective of study was to formulate Empagliflozin tamper resistant and any adulterant tablet after its manufacture is almost curtained to be observed. The developed tablets were evaluated for various compression characteristics like weight variation, friability, hardness and thickness.

MATERIALS AND METHODS

MATERIALS:

Empagliflozin was obtained from Aurobindo Pharma Ltd., Hyderabad. Microcrystalline cellulose, magnesium stearate, cross-povidone, lactose, talc were procured from Signet Chemicals Pvt. Ltd., Mumbai.

METHODS:

Solid dispersion technology:

a) Fusion method:

Accurately weighed Empagliflozin (2.5gm) and selected polymer PEG 6000, Plasdone S 630 (2.0gm) at 1:2 ratio and fused in a china dish with stirring. Immediately cooled the fused solid dispersion under running water or using cool water. Resulting cooled solid dispersion was subjected to mill into small granules and sifted granules through mesh #20.

b) Solvent evaporation method:

Solid dispersion of empagliflozin in PEG 6000 and plasdone S 630 was prepared in the ratio (1:4) by using solvent evaporation method. Empagliflozin was dissolved in an appropriate amount of ethanol/methanol (2.5 to 3.0 of times the total weight of drug and polymer). After complete dissolution, solutions were transferred into a container in which the polymeric carriers PEG-6000 and plasdone S630 were present and solvent was evaporated at 45 to 50°C and resulting residue was dried in hot air oven for 1h and stored for 24h in a desiccator. Subsequently, the dispersion was grounded in a mortar and passed through mesh #20.

A) Pre-formulation Parameters:

a)Bulk density (gm/ml):

Bulk density of a compound varies substantially with the method or crystallization, milling or formulation. Bulk density was determined by pouring pre-sieved blend into a graduated cylinder via a large funnel and the volume and weight were measured.

b)Tapped density:

Tapped density was determined by placing a graduated cylinder containing a known mass of blend and mechanical tapper apparatus. This was operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume. The tapped density was computed using formula:

Tapped density= weight of blend/tapped volume of blend

c) Carr's compressibility index:

Carr's index was measured using the values of bulk density and tapped density. The following equation was used to find the Carr's index.

Carr's index= (tapped density- bulk density)/tapped density × 100

d) Hausner's ratio:

It indicates the flow properties of powder and ratio of tapped density to the bulk density of the powder or blend.

Hausner's ratio= tapped density/ bulk density

e) Angle of repose:

The manner in which stresses are transmitted through a bead and the beads response to applied stress is reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder on a conical heap on a level flat surface and measure the included angle with the horizontal.

$$\tan ø = h/r$$

Where, h= height of the heap, r= radius of the heap.

B) Post compression parameters:

a) Hardness test

This is the force required to break a tablet in diametric compression. Hardness of the tablet was determined by Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture.

b) Tablet Size and Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet was measured by Vernier Callipers scale. The thickness of the tablet related to the tablet hardness and can be used as initial control parameter. Tablet thickness should be controlled within a ±5%. In addition, thickness must be controlled to facilitate packaging.

c) Friability

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets was taken and was placed in the Friabilator and rotated at 25rpm for 4min. The difference in the weight was noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

$$\% \text{ friability} = (w_1 - w_2)/w_1 \times 100$$

Where w_1= weight of tablets before test

W_2= weight of tablets after test.

d) Weight Variation of Tablets

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits. Twenty tablets were taken randomly and weighed accurately. The average weight was calculated by:

Average weight = weight of 20 tablets /20

e) Dissolution Method

Dissolution media was taken as water, 900ml placed in the vessel and the USP apparatus –II (paddle) was assembled. The medium was allowed to equilibrate to temp of 37+0.5°C. Tablet was placed in the basket and placed in the vessel; the apparatus was operated at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fluid was replaced. The samples were analysed using UV.

RESULTS AND DISCUSSION

Absorbance value of drug in pH 6.8 Phosphate buffer

Table: 1 Standard Calibration Curve of Empagliflozin

Sr. No.	Concentration (µg/ml)	Absorbance (272nm)
1	0	0
2	2	0.095
3	4	0.197
4	6	0.291
5	8	0.394
6	10	0.508

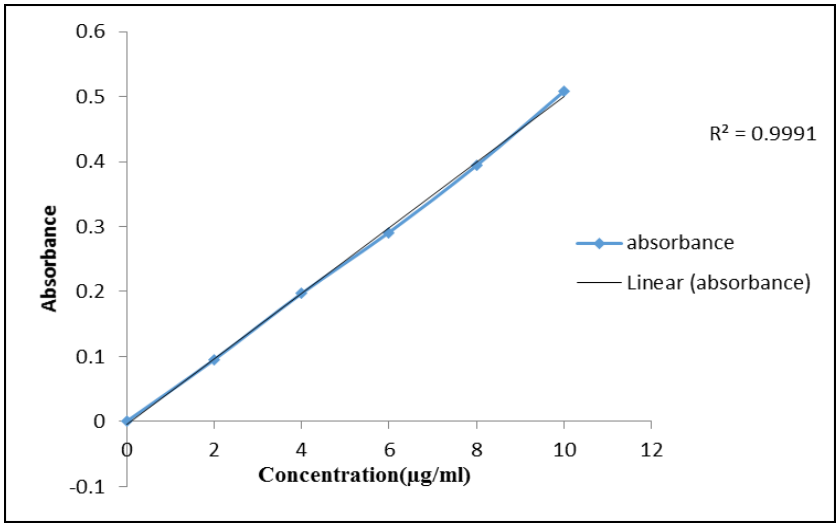

Fig. 1: Standard plot for Empagliflozin immediate release tablets

Five formulations of immediate release tablets were developed employing different proportions from F1-F5. In the pre-formulation studies, the Micromeritic flow properties of the Blend were assessed by determining angle of repose, compressibility index, and Hausner's ratio. All the finished products were evaluated for thickness, hardness, friability, weight variation and dissolution rate. Dissolution rate study was performed in 900 ml using USP-II (paddle) apparatus.

a) Angle of repose:

The values obtained for Angle of repose for all formulations are tabulated in table, the values were found in the range from indicate good flow Property of the power blend shown in Table 2.

b) Carr's index & Hausner's ratio: Carr's index and Hausner's ratio values range between respectively indicating that the powder blends have the required flow property for direct compression shown in Table 2.

c) Bulk density & Tapped density:

Bulk density and Tapped density values were within the limits indicating that the powder blends have the required flow for direct compression shown in Table 2.

Table 2: Pre-compression parameters

Formulation	Bulk density(gm/cc)	Tapped density (gm/cc)	Angle of repose	Carr's index	Hausner's ratio
F1	0.571	0.6	29.299	5.26	1.05
F2	0.551	0.585	31.693	21.81	1.05
F3	0.536	0.568	29.509	10.67	1.12
F4	0.581	0.623	26.390	6.89	1.06
F5	0.368	0.553	39.680	32.7	1.52

Post compression evaluation studies:

a) Weight Variation

All tablets passed weight variation tests as the % variation was within the pharmacopeia limits and weight of all tablets was found to be uniform with low standard deviation. Drug content of all batches was within the acceptable range which shows the proper mixing of drug with the excipients. Results are shown in Table 3.

b) Hardness

Hardness was found to be within the range, indicates that these tablets have good mechanical strength with sufficient hardness. Results are shown in Table 3.

c) Friability

Friability values were found to be less than 1% in cases and considered to be satisfactory. Results are shown in Table 3.

Post compression parameter of immediate release tablets of Empagliflozin prepared by direct compression method:

Table 3: Post compression parameters

Formulations	% of weight variation(mg)	Thickness (mm)	% of friability	Drug content %	Hardness ($kg/cm^{2)}$
F1	245.21	3.9	0.0481	99.35± 1.14	3.5
F2	249.28	4.0	0.0566	99.28± 0.80	3.5
F3	235.29	4.0	0.0639	99.12± 2.47	3.8
F4	247.58	3.9	0.0477	99.53± 1.87	3.5
F5	250.04	3.9	0.0681	98.57±1.22	3

Dissolution Studies

The dissolution studies for the optimized formulation and the marketed formulation was compared. Results showed that %cumulative releases of optimized (F4) formulation were same as that of marketed product. Results are shown in Table 5.

Table 4: Composition of Empagliflozin immediate release tablets

Sr. No.	Ingredients/ Formulations	F1	F2	F3	F4	F5
1	Empagliflozin	100	100	100	100	25
2	MCC	69	69	69	69	105
3	Lactose	69	69	69	69	105
4	Crospovidone	9.0	9.0	9.0	9.0	1.2
5	Talc	1.5	1.5	1.5	1.5	1.5
6	Magnesium stearate	1.5	1.5	1.5	1.5	1.5
7	Core tablet weight(mg)	250	250	250	250	250

Table 5: Drug release profile Empagliflozin immediate release tablets

Time (min)	F1	F2	F3	F4	F5
00	00000000	0	0	0	0
10	25.2±0.8	25.1±0.2	25.3±1.4	27.3±0.4	26.2 ±0.2
20	42.3±0.4	46.3±1.2	43.5±1.1	45.5±2.3	50.4 ±0.12
30	67.3±1.4	68.6±2.3	66.6±0.7	68.6±1.1	60.6 ±1.6
40	79.4±1.8	74.8±0.8	77.9±2.1	75.8±0.5	76.3 ±0.3
50	80.8±1.1	79.3±2.1	83.2±1.5	89.8±0.5	80.1 ±1.8
60	84.3±1.9	82.0±2.6	91.2±1.6	95.8±1.4	93.8 ±2.7

Percentage Cumulative Drug Release From Various Formulations:

A) *In-vitro* Release data of Empagliflozin F1 and F2 using PEG-6000 and Plasidone-S-630 by Fusion method

Table: 6. *In-vitro* release data of formulations F1 and F2

Time in (min)	F1	F2
0	0	0
10	25.2±0.8	25.1±0.2
20	42.3±0.4	46.3±1.2
30	67.3±1.4	68.6±2.3
40	79.4±1.8	74.8±0.8
50	80.8±1.1	79.3±2.1
60	84.3±1.9	82±2.6

All **v**alues represent mean cumulative percent drug released ± SD (n=6)

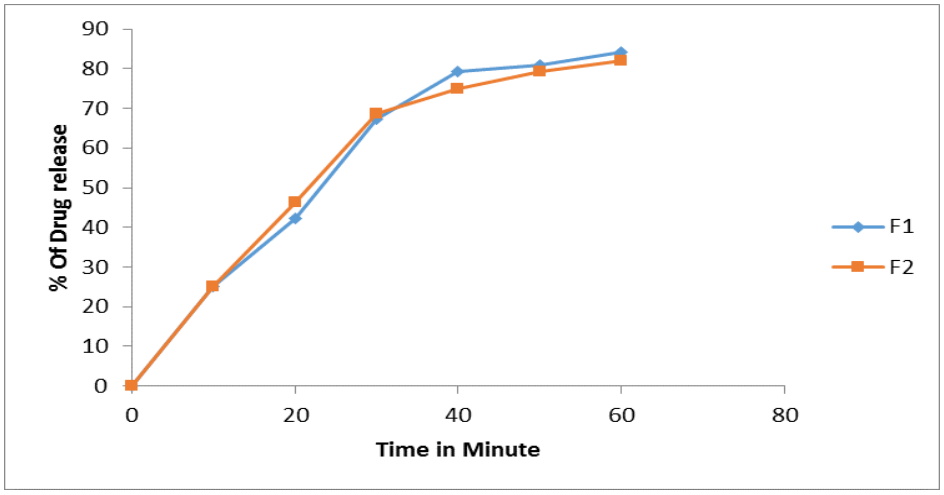

Figure 2: *In-vitro* release of formulations F1 and F2 of Fusion method using PEG-6000, Plasidone-S-630

B) *In-vitro* Drug release data of Empagliflozin F3, F4 of Solvent evaporation Technique PEG-6000, Plasidone-S-630

Table 7: *In-vitro* Drug release data of Empagliflozin F3, F4 of Solvent evaporation Technique using PEG-6000, Plasidone-S-630

Time (min)	F3	F4
0	0	0
10	25.3±1.4	27.3±0.4
20	43.5±1.1	45.5±2.3
30	66.6±0.7	68.6±1.1
40	77.9±2.1	75.8±0.5
50	83.2±1.5	89.8±0.5
60	91.2±1.6	95.8±1.4

All **v**alues represent mean cumulative percent drug released ± SD (n=6)

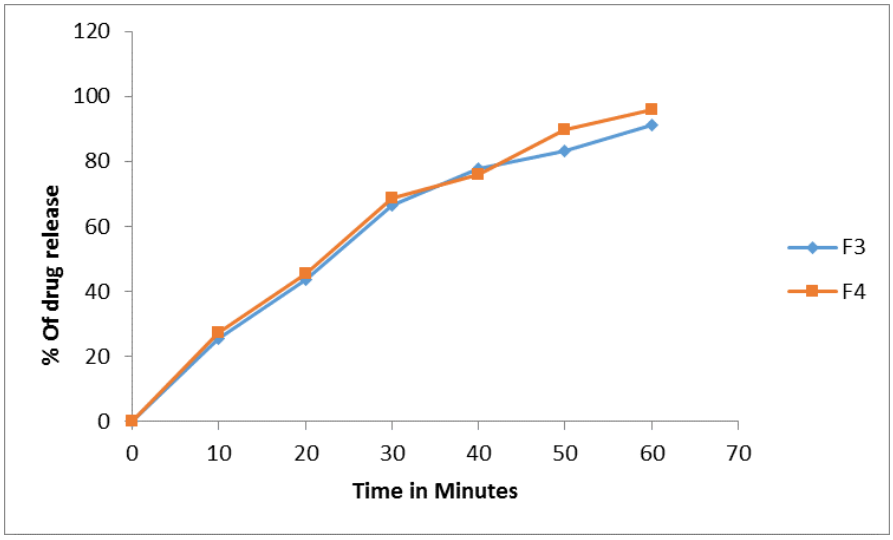

Figure 3: *In-vitro* Drug release data of Empagliflozin F3, F4 of Solvent evaporation Technique using PEG-6000, Plasidone-S-630

C) *In-vitro* Drug release data of Empagliflozin F5 Tablet

Table 8: *In-vitro* Drug release data of Empagliflozin F5 Tablet

Time (min)	F5
0	0
10	26.2 ±0.2
20	50.4±0.12
30	60.6±1.6
40	76.3±0.3
50	80.1±1.8
60	93.8±2.7

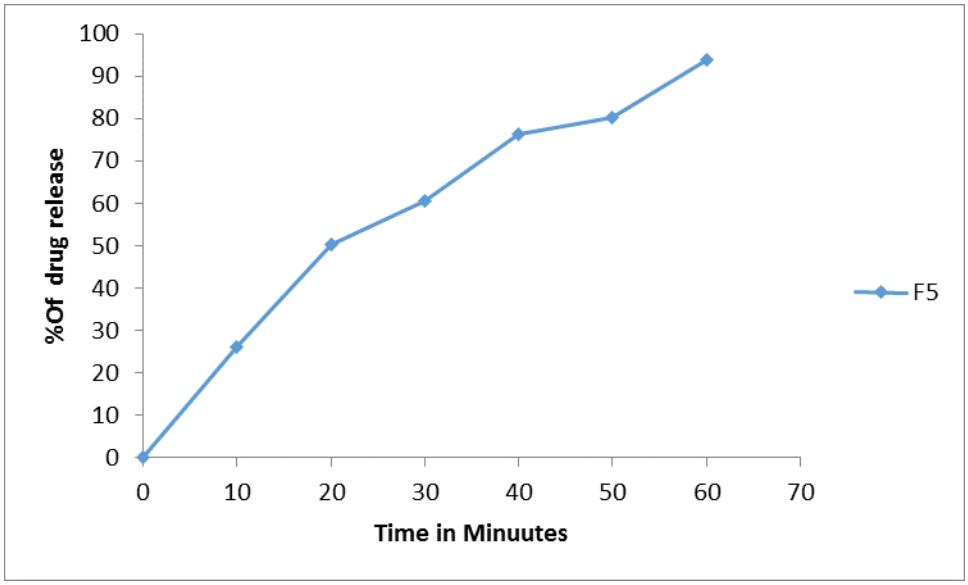

Figure 4: *In-vitro* Drug release data of Empagliflozin F5 tablet

Table 9: Release for Empagliflozin immediate release tablets of various formulations F1 to F5

Time (mins)/%C	F1	F2	F3	F4	F5
0		0	0	0	0
10	25.2±0.8	25.1±0.2	25.3±1.4	27.3±0.4	26.2 ±0.2
20	42.3±0.4	46.3±1.2	43.5±1.1	45.5±2.3	50.4 ±0.12
30	67.3±1.4	68.6±2.3	66.6±0.7	68.6±1.1	60.6 ±1.6
40	79.4±1.8	74.8±0.8	77.9±2.1	75.8±0.5	76.3 ±0.3
50	80.8±1.1	79.3±2.1	83.2±1.5	89.8±0.5	80.1 ±1.8
60	84.3±1.9	82.0±2.6	91.2±1.6	95.8±1.4	93.8 ±2.7

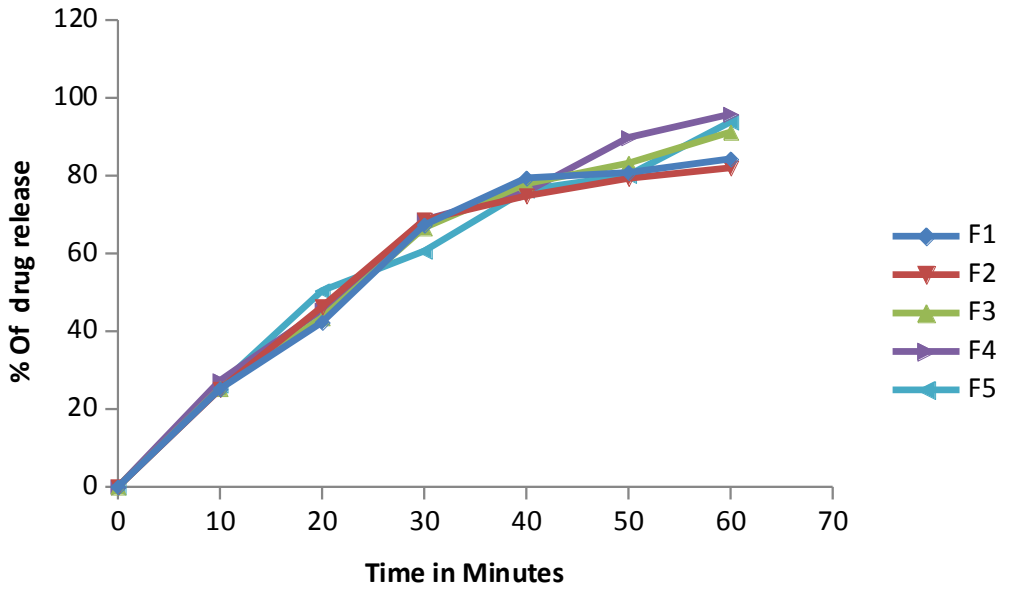

Figure 5: *In-vitro* Dissolution profile of Empagliflozin for various formulations F1-F5

% CDR of pure drug and F4

Table 10: % CDR of pure drug versus F4 formulation

Sr. No.	% CDR of Pure drug	F4
1	29.8	27.3
2	48.5	45.5
3	72.9	68.6
4	79.8	75.8
5	91.5	89.8
6	96.5	95.8

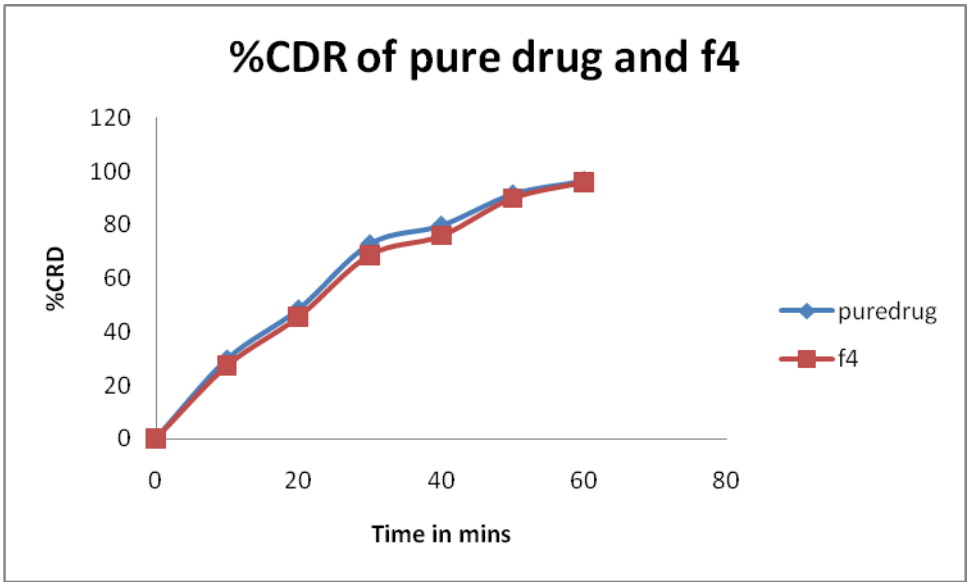

Figure 6: %CDR of pure drug and F4

The pure drug empagliflozin percentage drug release was found to be 96.5 % at the end of 60mins. F4 formulation showed 95.8% drug release at the end of release time.

Formulation F1

Composed of Drug and polymer 1:1 ratio, failed to release the minimum amount of drug. It releases only 84.3% of the drug in 1 hour. Drug release was too low, further improved in next trail.

Formulation F2

Composed of Drug and polymer 1:1 ratio, failed to release the minimum amount of drug. It releases only 79.2% of the drug in 1 hour. Drug release was too low, further improved in next trail.

Formulation F3

Here polymer concentration was increased to 1:1 ratio prepared by Solvent Evaporation method, results 91.2% % of drug release. Drug release further improved in next trail.

Formulation F4

Here polymer concentration was increased to 1:1 ratio prepared by Evaporation method, results 98.5% of drug release. So F4 was considered as optimized formulation.

Formulation F5

In this formulation, 4.8% Cross Povidone as used and % drug release was found to be 93.8 %. Hence this formulation was also found to be convenient.

Hence F4 was found to be optimized formulation in solvent evaporation method which releases 95.8% drug as compared to plain tablet of solid dispersion technique.

Fourier Transform Infrared Spectroscopy (FTIR):-

FTIR spectra of the drug and the optimized formulation were recorded in range of 400-4000cm^{-1}.

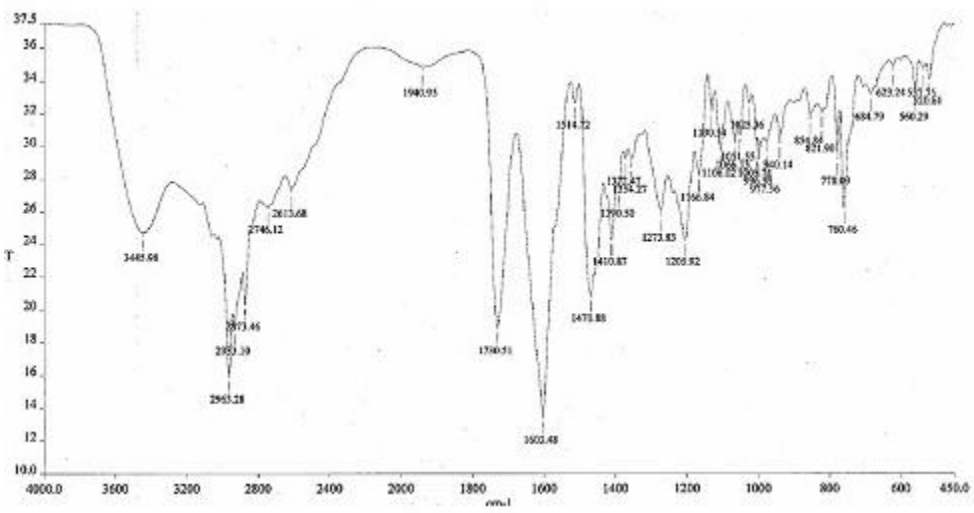

Figure 7: FTIR spectra of the drug

FTIR Spectroscopy of API

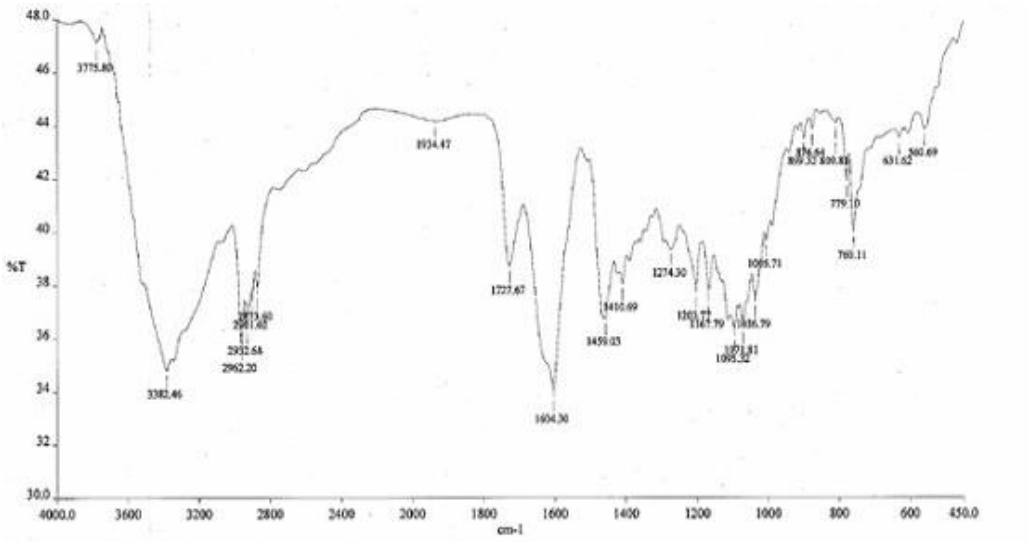

Figure 8: FTIR Spectroscopy of API

IR Spectra of API and Excipients mixtures:

Table 11: IR Spectra of API and Excipients mixtures

API Wave number in cm^{-1}	Functional groups	peak observed in API + Excipients
3445.98 cm^{-1}	Amine (NH)	3382.46cm^{-1}
2963.28cm^{-1}	C=N	2962.20cm^{-1}
1730.51 cm^{-1}	Carboxylate	1727.67cm^{-1}
1603.48 cm^{-1}	C=O	1604.30cm^{-1}
1066.13cm^{-1}	C-N	1071.81cm^{-1}

The functional groups present in the drug were identified. The FTIR of Empagliflozin showed intense bands at 3445.98 cm-1, 2963.28 cm-1, 1730.51 cm-1, 1603.48 cm-1 and 1066.13 cm-1 cores ponding to the functional groups NH, C=N, Carboxylate=O and CN bending respectively. The wave numbers of drug were compared with final formulated product IR spectrum. The FTIR spectra of Empagliflozin, Empagliflozin with excipients mixture. The results revealed that there was no significant disturbance in the principle peaks of pure drug Empagliflozin. The FTIR spectrum for Empagliflozin and excipients mixture reveals a broad peak at 3382.46 cm-1 due to N–H bond stretching. From the interpretation, it was understood that there was no major shifting in the frequencies of Empagliflozin which

indicated that there is no chemical interaction in the formulations. This further confirms the integrity of pure drug and compatibility of it with excipients.

Table 12: Kinetic values obtained from different plots of formulation F4

Formulation	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Peppas (r^2)
F1	0.9548	0.9508	0.9875	0.9865

CONCLUSION

Present study was aimed to develop and evaluate anti-diabetic immediate release oral tablet of Empagliflozin. On the basis of literature survey and Compatibility Tests, excipients like Microcrystalline Cellulose, cross povidone, lactose, Magnesium Stearate, talc were used. In present study, the tablets were prepared by using direct compression technique. In order to optimize the product, different formulations were developed. All the formulations were evaluated for physical characteristics, *in-vitro* dissolution studies. The blends were analysed for the parameters such as Bulk density, Tapped density, Compressibility index, Hausner's ratio, Angle of repose and results were found to be within the limits. Based on the results of dissolution studies and marketed formulation, F4 was found to be the best among trails.

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