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DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLETS OF DAPAGLIFLOZIN FOR TYPE 2 DIABETES

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Abstract:

The objective of the present study was to formulate sustained-release matrix tablets of Dapagliflozin, for treatment of to manage type 2 diabetes. The matrix tablets were prepared by direct compression method using various synthetic polymers in various concentrations. The powder showed satisfactory flow properties and compressibility. All the formulations showed acceptable pharmacopoeia standards. The result of formulation F3. Successful formulation was found stable after evaluation for physicochemical parameters when kept for 90 days at 40^{0}C ±20C, 75% ± 5% RH for 3 months. It concluded that sustained release matrix tablets of Dapagliflozin containing Eudragit RS100 provide a better option for the Sustained release of the drug.

Keywords: *Dapagliflozin, Polymers, FTIR Studies, Direct compression technique, Sustained release matrix tablets, In vitro drug release studies.*

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INTRODUCTION:

Sustained Drug Delivery System:

Over the past 30 years, as the expense and complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries.

With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic fir an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after adminisatration of a single dose. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT.

Physician can achieve several desirable therapeutics advantages by prescribing sustained release dosage form. Since, the frequency of drug administration is reduced, patient's compliances can be improved and the drug administration can be made more convenient as well. The blood level oscillation characteristics of multiple dosing form of conventional dosage form is reduced, because more even blood level is maintained in the design of sustained release dosage form. The total amount of drug administered, thus maximum availability with a minimum dose. In addition, the safety margin of high potency drug can be increased and the incidence of both local and systemic adverse effects can be reduced in sensitive patients. Overall, increased administration of sustained release dosage form gives increased reliability. Not all the drugs are the suitable candidates for the sustained release dosage form. Ideal characteristic of the drug for the sustained release dosage form are;

- Drug should have a shorter half-life as drug with a longer half-life are inherently long acting drugs.
- Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur through the gut.
- Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.
- Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form.

Potential Advantage Of Sustained Release Dosage Form:

- Avoid patient's compliance problem due to reduced frequency of dosing.
- Blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced because a more even blood level is maintained.
- Employ a less total drug.
- Minimize or eliminate local or systemic side effects.
- Minimize drug accumulation with chronic dosing.
- Obtained less potential of reduction in drug activity with chronic use.
- Improved efficiency in treatment.
  - Cure or control condition more promptly.
  - Improved control of condition i.e. reduced fluctuation in drug level.
  - Improved bioavailability of some drugs.
- Make a use of special effects, e.g sustained release aspect for relief of arthritis by dosing before bedtime.
- Economy.
- Overall, administrations of sustained release form enable increased reliability of therapy.

MATERIALS:

Dapagliflozin was procured from Synpharma Research Labs, HYD, Eudragit RS100, Ethyl cellulose, Micro crystalline cellulose , Magnesium Stearate and Talc were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy Rivaroxaban discs were created by compressing the Rivaroxaban with KBr and the spectra was scanned in the range between 4000 to 400 cm-1. Perfect operational conditions were maintained. The absorption maxima which is denoted as max in spectrum obtained with the drug substance is compared with the intensity to those of reference spectrum.

Preparation of Dapagliflozin tablets:

Table-1: Formulation Table of Dapagliflozin sustained release tablets

S.NO.	INGREDIENTS	F1	F 2	F 3	F 4
1	Dapagliflozin	20	20	20	20
2	Eudragit RS100	25	50	-	-
3	Ethyl cellulose	-	-	25	50
4	Microcrystalline Cellulose	150	125	100	75
5	Magnesium stearate	3	3	3	3
6	Talc	2	2	2	2
7	Total Wt.	200	200	200	200

Direct compression technique

Sustained release matrix tablets of Dapagliflozin were prepared by direct compression. All the ingredients were passed through 40-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200mg using 10mm round flat punches on 8-station rotary tablet machine (Rimek).

Evaluation studies

1.Pre-compression parameters

Determination of bulk density and tapped density

a) Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (vo) was measured. Then the cylinder was dropped at 2-second intervals onto a hard-wooden surface three times, from a height of one inch. The volume was recorded and the bulk density was calculated.

b) Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (vo) was measured. Then the surface was carefully smoothed and the volume was measured. Tap density was calculated by measuring final volume (Vf) after 50 taps on wooden surface from 6 inch height and was expressed in g/cm3 .

Bulk density = W/Vo

Tapped density = W/Vf

Where,

Vo = initial volume

Vf = final volume.

Compressibility index and Hauners ratio

The Compressibility index and Hauners ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and Hausner ratio.

Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\tan\theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where

h = height of pile

r = radius of the base of the pile

θ = angle of repose

Post compression parameters

Weight variation:

Method:

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in Table No 1 and none deviate by more than twice the percentage shown.

Table-2: Percentage deviation allowed under weight variation

Percentage deviation allowed under weight variation test.	
Average weight of tablet (X mg)	**PERCENTAGE DEVIATION**
130 mg or less	**10**
130mg to 324 mg	**7.5**
more than 324 mg	**5**

Thickness:
Twenty tablets were randomly selected form each batch and there thickness was measured by using Vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness:
Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability:
Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

Content Uniformity:
The drug content directly relates to the pharmacological efficacy, so it is mandatory to do the drug content test. It is an official quality control test. The drug content in all formulations were analyzed by triturating 20 tablets in mortar and pestle, then from the powder 75 mg equivalent of Sitagliptin was taken and transferred to 100ml standard volumetric flask. Then the volume was prepared to 50ml with pH 6.8 phosphate buffer. This was shaken for 15 min to mix. Then the volume was prepared to 100ml with phosphate buffer. The solution was strained by using whatmann filter paper and then it is diluted and absorbance was determined by using UV-Visible spectrophotometer at 276 nm using pH 6.8 phosphate buffer as blank.

Disintegration time:
The disintegration time of tablets was determined by using Disintegration test apparatus (scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.

In- Vitro Release study:
In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 100 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time. Temperature maintained at 37□5.The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask and make the volume with distilled water. The diluted samples were assayed at 276 nm against reagent blank.

Stability studies:
The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared Matrix tablets of Dapagliflozin were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2oc and refrigerator 2-8oc for a period of 90 days.

RESULTS AND DISCUSSION:

FT-IR Spectrum of Dapagliflozin

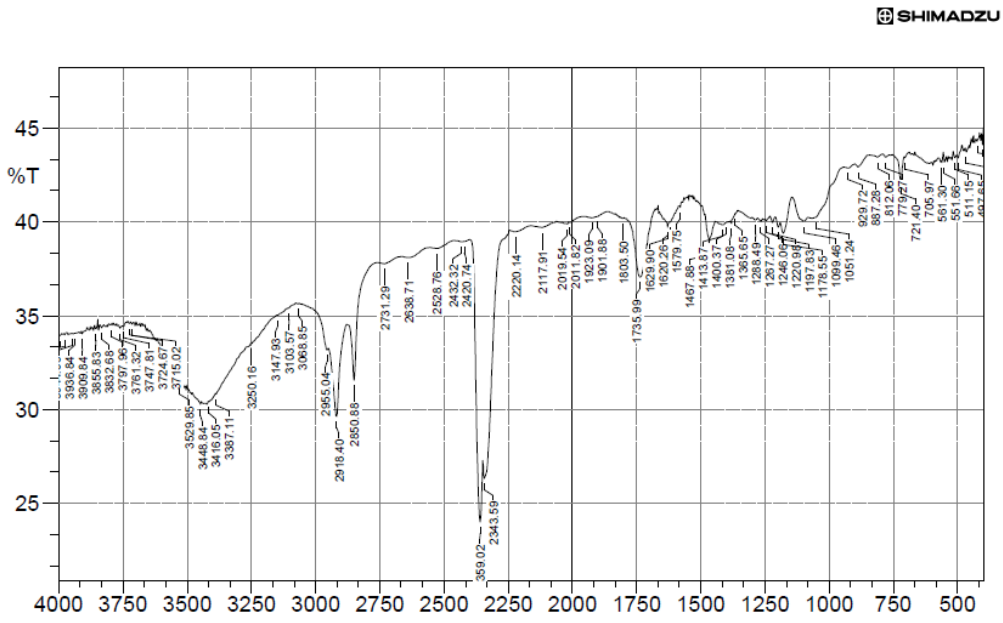


Fig-1: FTIR Spectra of Dapagliflozin

Table-3: Characteristic Peaks and frequency of Dapagliflozin

S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	4000-3500	3902.75
2	OH Bending	1500-1000	1204.65
3	C-H stretching	3000-2500	2839.31
4	C=O stretching	2000-1500	1599.93

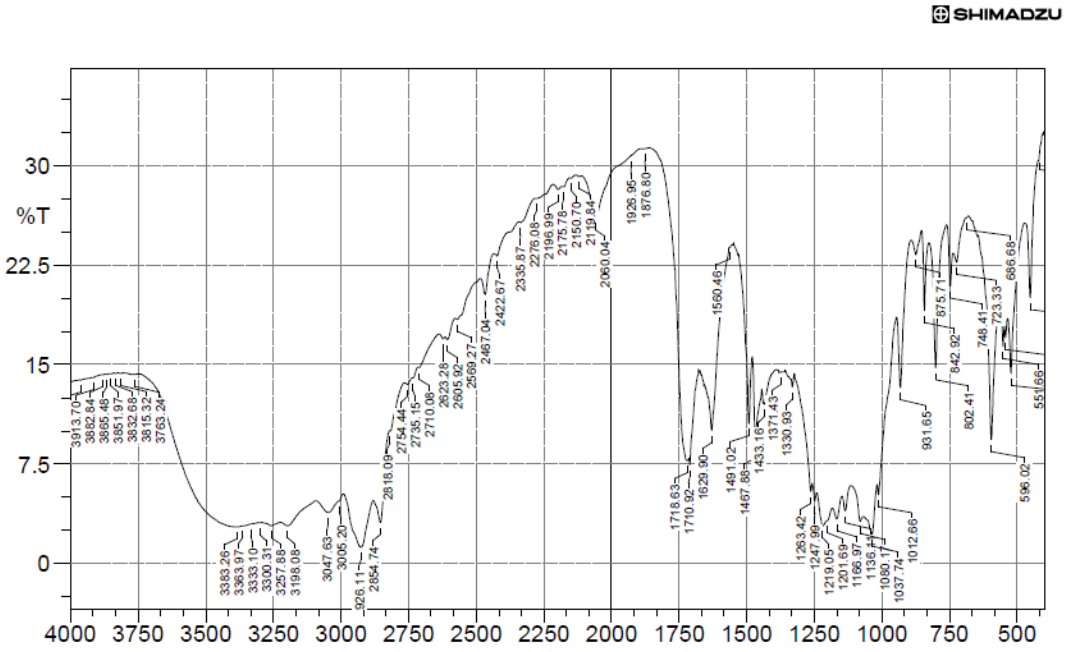


Fig-2: FT-IR graph for optimized formulation

Table-4: Characteristic Peaks for optimized formulation

S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3500-3000	3333.10
2	OH Bending	2750-2500	2710.10
3	C-H stretching	1500-1000	1263.45

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

EVALUATION STUDIES
Pre compression Parameters

Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.569-0.574.

Tapped density: The tapped density for the formulated blend was carrie out for all formulation and found in the range of 0.612-0.620.

Angle of repose: The angle of repose for the formulated blend was carried out and the results were shown in Table. It concludes that all the formulations blend was found to be in the range of 26^0 to 30^0

Compressibility index: Compressibility index was carried out, it found between 10% to 14.27 % indicating the powder blend have the required flow property for compression.

Hauser ratio: Hauser ratio was carried out, it found between 1.17 to 1.21 indicating the powder blend have the required flow property for compression.

Table-5: Results of Pre-compression parameters of tablets

F. No	Bulk density	Tapped density	Compressibility index	Hauser ratio	Angle of repose (0)
F1	0.569	0.612	13.24	1.17	30^0
F2	0.574	0.618	14.23	1.20	28^0
F3	0.563	0.620	13.58	1.19	27^0
F4	0.572	0.605	14.27	1.21	26^0

Post compression parameters
Weight variation:
All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:
Tablets mean thickness were uniform in F1 to F4 formulations and were found to be in the range of 2.1 mm to 2.6 mm.

Hardness:
The measured hardness of tablets of each batch ranged between 3.2 to 3.6 kg/cm^2. This ensures good handling characteristics of all batches.

FRIABILITY:

The % Friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:
The percentage of drug content for F1 to F4 was found to be between 86.29 % to 90.10 % of Dapagliflozin, it complies with official specifications.

Disintegration Time:
In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods.

Table-6: Evaluation parameters of Dapagliflozin SR tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time (min)
F1	200	2.1	3.2	0.26	86.29	14
F2	199	2.4	3.5	0.31	88.42	12
F3	200	2.5	3.3	0.29	90.10	9
F4	200	2.6	3.6	0.35	89.28	13

Dissolution studies

All the 4 formulation of Dapagliflozin tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-7: Drug release studies of all formulations

Time	F1	F2	F3	F4
0	0	0	0	0
1	17.82	18.10	19.10	17.89
2	25.87	27.2	29.76	28.49
3	38.10	37.58	39.58	38.12
4	58.25	55.48	59.82	58.13
5	69.79	68.12	68.43	67.43
6	72.10	73.56	78.82	75.86
7	83.25	84.97	86.40	85.46
8	94.63	95.86	98.85	97.85

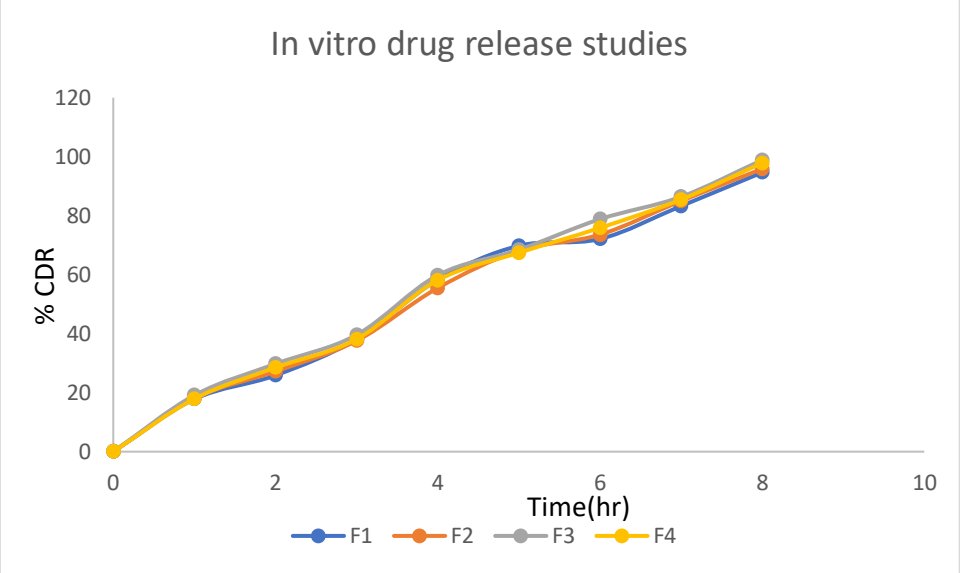


Fig-3: Dissolution Profile of F1 to F4 formulations

Cumulative Drug release of F3 formulation shows 98.85 % within 8 hr. better drug release when compared with other formulations.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 90 days. Parameters quantified at various time intervals were shown.

Table-8: Stability studies of all formulations

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	**25^{0}C/60%RH % Release**	98.85	97.81	96.83	95.48	**Not less than 85 %**
F-3	**30^{0}C/75% RH % Release**	98.85	97.13	96.43	95.52	**Not less than 85 %**
F-3	**40^{0}C/75% RH % Release**	98.85	97.10	96.12	95.10	**Not less than 85 %**

SUMMARY AND CONCLUSION:

Sustained release dosage forms are the most popular drug delivery systems due to their biopharmaceutical and pharmacokinetics advantages over conventional dosage forms. The development of an improved pharmaceutical dosage form, such as an oral sustained release preparation, should be based upon the pharmacokinetic and pharmacodynamics properties of the drug. Studies have been carried out for developing Sustained release matrix tablet formulations of Dapagliflozin by using various polymers. These were selected as matrix forming polymers for sustained release as these were reported to have matrix forming properties. These sustained release matrix tablets prepared by using direct compression technique. The prepared matrix tablets were evaluated for weight uniformity, hardness, friability and drug content. The matrix tablets were then evaluated by in vitro dissolution studies. Selected formulations of Dapagliflozin were subjected to accelerated stability studies. The formulations were stored at 40^{0}C ±20C, 75% ± 5% RH for 3 months. During the accelerated storage condition the tablets were evaluated for physical parameters such as weight uniformity, hardness, friability, drug content and for drug release before and after storage.The results of the present study indicate that sustained release tablets of Dapagliflozin with sustained drug release can be successfully prepared by direct compression method using Eudragit RS 100 and Ethyl cellulose.The formulation F3 containing Eudragit RS100 was found to be promising, which shows an in vitro drug release of 98.85% in 8 h along with satisfactory results.From the above experimental results, it can be concluded that sustained-release tablets of Dapagliflozin can be prepared by using different proportions & combination of Excipients and we selected F3 as the best formulation based on dissolution profile and physical characteristics. Formulation (F3) showed total drug release in 8 hr and showed fair flow properties when compared to other formulations.

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