IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF PULSATILE DRUG RELEASE TABLETS

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Abstract- The major goal of this study is to develop and test a pulsatile drug delivery system for the medication Dapagliflozin in order to achieve time-specific release. The PDDS (Pulsatile Medicine Delivery System) delivers the drug at the correct time, right place of action, amount, providing greater benefits than traditional dose forms and boosting patient compliance. These systems are designed to work with the body's circadian rhythms, and the medicine is released as a pulse after a lag period. A Dapagliflozin rapid disintegrating core tablet was made utilising Croscarmellose sodium (MCC), Lactose, Talc, and Magnesium stearate in a direct compression process. The core tablet was then coated using a press coating procedure with a mixture of Ethyl Cellulose (EC), a hydrophobic polymer, and Hydroxypropyl Methyl Cellulose (HPMC), a hydrophilic polymer. Various weight ratios of Hydroxypropyl Methyl Cellulose (HPMC K4M) and Ethyl Cellulose (200:0, 150:50, 100:100, 50:150, 0:200) were pressed coated over Dapagliflozin core tablets to release Dapagliflozin after a 4 hour lag period. The pre-compression and post-compression characteristics of prepared tablets were assessed. The best results were obtained in formulations containing 50:50 weight ratios of HPMC K4M and Ethyl Cellulose. This is a viable formulation for Dapagliflozin pulsatile medication delivery in diabetes. Using an equal blend of Hydroxypropyl Methyl Cellulose and Ethyl Cellulose, a pulsatile drug delivery system for Dapagliflozin and other medicines can be produced.

Key words- **Pulsatile drug delivery system, Dapagliflozin, Hydroxypropyl methyl cellulose, Ethyl cellulose, Core tablet and Press coating technique.**

I. INTRODUCTION:

The fastest growing, largest, and oldest segment of drug delivery market is oral medication administration system. [1] Pharmaceutical market has shown a growing preference for regulated and targeted medication delivery systems; designed to deliver therapeutic agents to specified sites/organs in a consistent, variable, and sustained manner. [2] Sickness follows a predictable cyclic pattern, thus scheduling pharmaceutical regimens can improve the outcome of a desired impact. This condition necessitates the delivery of the medication as a "pulse" after a lag period, and the design must ensure that the drug is released completely and quickly.[3] Pulsatile medication delivery holds promise for disorders such as asthma, heart attack, peptic ulcer, diabetes, and hypercholesterolemia. [4] Pulsatile drug advantages: increased activity, reduced side effects, dosage frequency, dose size, improved patient compliance, lower daily cost to patient, drug adapts to circadian rhythms of body functions or diseases, drug targeting to specific sites such as the colon, and so on. Lack of manufacturing repeatability and efficacy, increased number of variables, numerous formulation procedures, higher production costs, requirement for advanced technology and trained/skilled individual are all disadvantages. First pass metabolism, bilological toleration, unique chronopharmacological needs, local therapeutic need, stomach irritation, or drug istability gastric fluid are all PDDS requirements. [5] The time controlled drug delivery system and the site specific drug delivery system are two forms of pulsatile drug delivery systems. [6] Goal of this research is to produce a Dapagliflozin pulsatile release formulation based on a swelling and erodible membrane technology that allows the medicine to be released after a predefined lag time.

I. MATERIALS AND EQUIPMENTS:

table no. 1: list of materials used for formulation of tablets

Sr. No.	*Materials*	*Source*
1.	*Dapagliflozin propanediol monohydrate*	*Pinnacle life sciences, Mumbai.*
2.	*Croscarmellose sodium*	*Vgi Pharma Pvt. Ltd., Akola*
3.	*Lactose*	*S.D. Fine Chem Lab Mumbai.*
4.	*Magnesium Stearate*	*S.D. Fine Chem Lab Mumbai.*
5.	*Talc*	*Loba chemie Pvt. Ltd. Mumbai*
6.	*Ethyl Cellulose*	*Colorcon Asia Pvt. Ltd.*
7.	*HPMC K4M*	*Research-Lab Fine Chem Industries Mumbai*

table no. 2: list of equipments used for formulation and evaluation of tablets

Sr. No.	*Equipment*	*Source*
1.	*Uv- visible spectrophotometer*	*UV-Shimadzu 1800*
2.	*Magnetic Stirrer*	*Remi, Mumbai.*
3.	*Mechanical Stirrer*	*Remi, Mumbai.*
4.	*Digital weighing Balance*	*Wensar ECB 300*
5.	*Friability Testing Apparatus*	*Panomex*
6.	*Hardness Tester*	*Pfizer hardness tester*
7.	*Microscrew Gauge*	*Mitutoyo, Japan.*
8.	*Dissolution test apparatus TDT-06PL*	*Electro lab Mumbai.*
9.	*FTIR*	*IR Affinity Shimadzu, Japan.*

II. PREFORMULATION STUDIES:[7]

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance, defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Objective of preformulation testing is to generate information useful to formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

Following pre-formulation studies were preformed:

1. **Identification of Pure Drug:**

   Identification of Dapagliflozin propanediol monohydrate was carried out by Infrared Spectroscopy.

2. **Melting point:**

   Melting point of Dapagliflozin propandiol monohydrate was determined by capillary method. Sufficient quantity of drug was filled in one side sealed capillary and melting point was recorded by thermometer with use of thial's tube.

3. **Solubility:**

   Solubility of Dapagliflozin proapanediol monohydrate was determined in methanol and ethanol. Solubility studies were performed by taking excess amount of Dapaglifozin propanediol monohydrate in different beakers containing the solvent.

4. **Determination of Absorption Maxima (λmax):**

   An absorption maximum of Dapagliflozin propanediol monohydrate was determined by scanning 10 µg/ml solution sample of drug at wavelength range from 200-400 nm using UV double beam spectrophotometer.

5. **Drug Excipient Compatibility Study:**

   Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the polymer. A physical mixture of drug and polymer in 1:1 ratio was prepared and mixed with suitable quantity of potassium bromide. The mixture was compressed to form a transparent pellet using a hydraulic press. It was scanned from 400 cm-1 to 4000 cm-1in a Shimadzu 8400 DRS FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks.\

ANALYTICAL METHOD:

Standard Calibration Curve of Dapaglifozin propanediol monohydrate:

10 mg of Dapaglifozin propanediol monohydrate was weighed into two different 10 ml volumetric flasks and volume was made up with methanol and phosphate buffer 6.8 respectively to prepare two primary (I) stock solutions.1ml of above solutions was individually pipette out in volumetric flasks and the volume was made up with methanol and phosphate buffer 6.8 respectively to form two different secondary (II) stock solutions. From the stock solution II, samples were withdrawn and diluted suitably with methanol and phosphate buffer 6.8 respectively to get the concentration range from 2 µg/ml to 10 µg/ml. The absorbance of these solutions was measured at 235 and 214.20 nm using methanol and phosphate buffer 6.8 as a blank respectively.

table no. 3: dilutions for calibration curve

Sr. No.	*Sample withdrawn from stock solution (ml)*	*Concentration (µg/ml)*
1	*0.2*	*2*
2	*0.4*	*4*
3	*0.6*	*6*
4	*0.8*	*8*
5	*1.0*	*10*

III. TABLET FORMULATION:

Preparation of Core Tablets of Dapaglifozin propanediol monohydrate

The core tablets were prepared by direct compression technique. The composition of the tablets was showed in Table No. 5.7. All the excipients were passed through sieve no.30. The required ingredients were accurately weighed and mixed thoroughly and dry blended with talc and magnesium stearate for 5 min. The resulting blends were subjected to the micromeritic properties and compressed by using 8 mm flat face punch using multi station tablet punching machine.[8]

table no. 4: formulation of dapagliflozin propanediol monohdrate core tablets

Sr. No.	*Ingredients*	*Batch*		
		C1	*C2*	*C3*
1.	*Dapagliflozin propanediol monohydrate (mg)*	*5*	*5*	*5*
2.	*Croscarmellose Sodium (mg)*	*4.3*	*6.5*	*9*
3.	*Magnesium stearate (mg)*	*1.5*	*1.5*	*1.5*
4.	*Talc (mg)*	*1.5*	*1.5*	*1.5*
5.	*Lactose (mg)*	*137.7*	*135.5*	*133*
	Total Wt. (mg)	*150*	*150*	*150*

Formulation of Press Coated Pulsatile Tablets of Dapaglifozin propanediol monohydrate:

Ingredients were weighed and passed through sieve no.70 and thoroughly mixed for 5 min. Initially half quantity of the mixture of polymers (hydrophilic HPMC and ethyl cellulose) was filled in the die of 12mm diameter and then gently compacted to make a powder bed with a flat surface. The die was filled with the remaining of coating mixture so that powder bed was compressed directly using 12mm flat punch to produce desired press coated tablets. Formulations of press coated tablet were shown in Table No. 5.8. The press coated tablets were further evaluated for hardness, thickness, content uniformity, friability and disintegration and dissolution time.[9]

table no. 5: composition of press coated tablets

Sr. No.	*Ingredients (mg)*	*Batch*				
		F1	*F2*	*F3*	*F4*	*F5*
1.	*Core Tablet*	*150*	*150*	*150*	*150*	*150*
2.	*HPMC k4m*	*200*	*150*	*100*	*50*	-
3.	*Ethyl Cellulose*	-	*50*	*100*	*150*	*200*
	Total Wt. (mg)	*350*	*350*	*350*	*350*	*350*

IV. EVALUATION:

A) Evaluation of Powder Blend [50,51,52,53,54]

1) 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.

2) 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.

3) Compressibility Index and Hausner Ratio:

Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. In a free-flowing powder, interactions are 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.

The compressibility index and Hausner ratio may be calculated using measured values for bulk density and tapped density as follows:

$$\text{compressibility index} = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \times 100$$

$$\text{Hausner ratio} = \frac{\rho_{tapped}}{\rho_{bulk}}$$

4) 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.

$$\text{Tan } \Theta = h/r$$

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

Where,

h = height of pile

r = radius of the base of the pile

Θ = angle of repose

B) Evaluation of Core and Press Coated Pulsatile Tablets [55,56,57,58]

1) Thickness:

Control of physical dimension of the tablet such as thickness is essential for consumer acceptance and tablet uniformity. The thickness of the tablet was measured using Microscrew gauge. It is measured in mm.

2) Hardness:

The Pfizer hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm2.

3) Friability:

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 mins dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were re- weighed and the percentage loss in tablet weight was determined.

% F = {1-(Wo/W)} ×100

Where,

% F = friability in percentage Wo = Initial weight of tablet

W = weight of tablets after revolution

4) Weight Variation Test:

The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The IP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the IP test if not more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit.

table no. 6: standard limit value in weight variation test (as per ip)

Average weight of a tablet	*Percentage Deviation*
80 mg or less	*±10*
>80 and <250mg	*±7.5*
250mg or more	*±5*

5) Uniformity of drug content:

Ten tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 7.4, the drug content was determined measuring the absorbance at 235 nm after suitable dilution using a UV/Visible Spectrophotometer.

6) Disintegration Test:

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in the USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of core tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing 7.4 phosphate buffer solution at 37 °C ± 1 °C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

7) In Vitro Drug Release Studies: [59]

Drug Release of the prepared core and press coated pulsatile tablets was determined using U.S.P. II (type II) dissolution rate test apparatus. The test was carried out in 900 ml of phosphate buffer pH 6.8 solution for subsequent hours. The test was performed at a temperature of 37± 0.5◦c and 50 rpm for 8 hours. Samples of 10 ml were withdrawn at known time intervals and were replaced with same volume of fresh dissolution media after each withdrawal. The samples were analyzed spectrophotometrically on double beam UV/Visible spectrophotometer at λ max 214.20 nm. The results in the form of percent cumulative drug released was calculated.

8) Stability Studies:

The accelerated stability studies were carried out according to ICH guidelines on optimized formulation. The formulation was packed in strip of aluminium foil and was stored in stability chamber maintained at 40° C and 75% RH (Zone III conditions as per ICH Q1 guidelines) for 1 month. The tablets were evaluated before and after 3 months for change in appearance, drug content and In-vitro release.

V. RESULTS AND DISCUSSSION:

Melting point:

Melting point of Dapaglifozin propanediol monohydrate was determined by capillary method. The melting point of Dapaglifozin propanediol monohydrate was found to be in the range 74-78°C, which complies with IP standards, indicating purity of the drug sample.

Solubility Analysis:

Dapaglifozin propanediol monohydrate was found to be rapidly soluble in ethanol and methanol.

Drug-Excipients Compatibility Study

FTIR Spectroscopy:

The IR spectrum of pure drug and polymer were studied. In the present study, it has been observed that there is no chemical interaction between Dapaglifozin propanediol monohydrate and polymer. It was observed that there were no changes in the main peak in IR spectra of mixture of drug and polymer which shows there were no physical interactions due to any bond formation between drug and polymer.

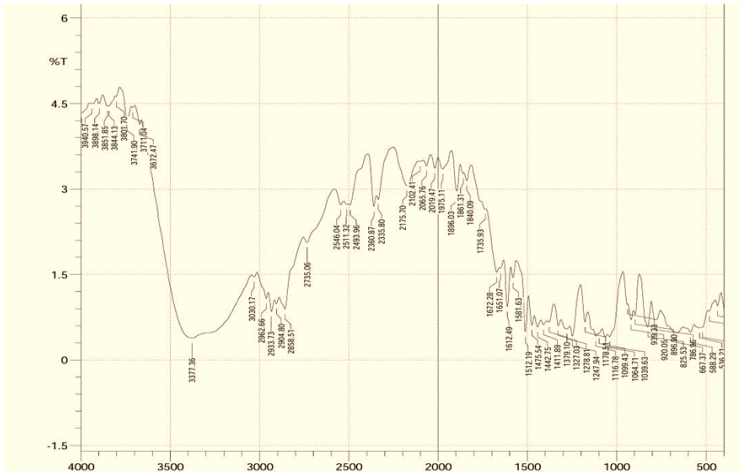

fig. no. 1: ftir spectra of pure drug dapaglifozin propanediol monohydrate

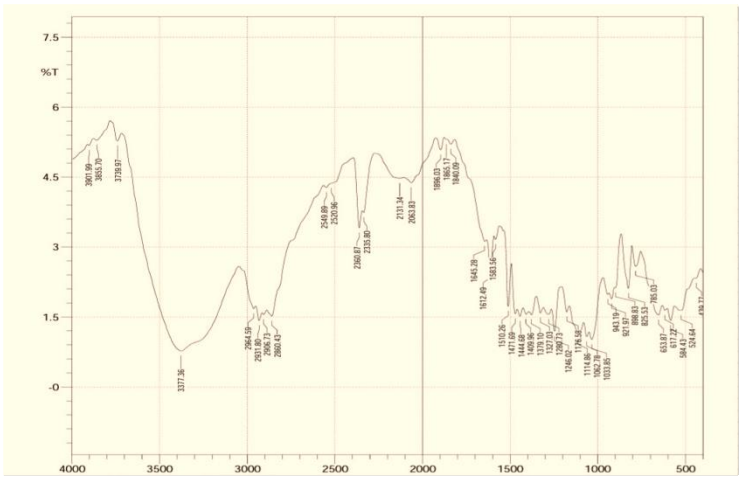

fig. no. 2: ftir spectra of dapaglifozin propanediol monohydrate+ hpmc k4m

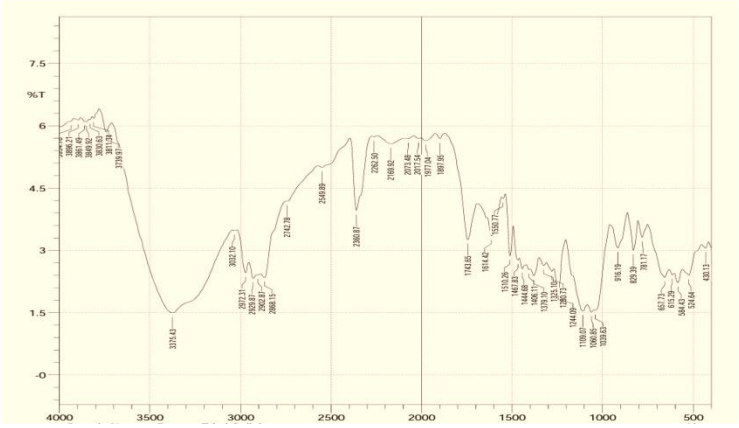

fig. no. 3: ftir spectra of dapaglifozin propanediol monohydrate and ethyl cellulose

Standard Calibration curve of Dapaglifozin propanediol monohydrate in methanol and phosphate buffer 6.8

The linearity of response of the drug was obtained at 2µg/ml to 10µg/ml concentrations. The calibration curve was obtained by plotting the absorbance versus the concentration data and was treated by linear regression analysis as shown in figure no. 4.

table no. 7: data for standard curve of dapaglifozin propanediol monohydrate in methanol and phosphate buffer 6.8

Sr. No.	*Conc. µg/ml*	*Absorbance (methanol)*	*Absorbance (PBS 6.8)*
1.	*2*	*0.131*	*0.013*
2.	*4*	*0.263*	*0.019*
3.	*6*	*0.397*	*0.028*
4.	*8*	*0.524*	*0.039*
5.	*10*	*0.662*	*0.044*

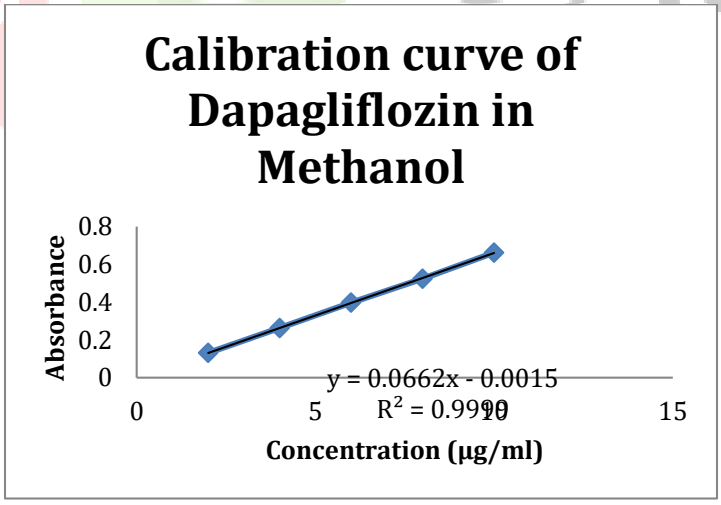

fig. no. 4: calibration curve of dapaglifozin propanediol monohydrate in methanol

Correlation Coefficient (R) = 0.9999

Equation for regression line: y = 0.066x - 0.0007-Where, X = Value of

Concentration

Y = Regressed value of Absorbance 0.066 = Slope of

regressed line 0.0007 = y intercept

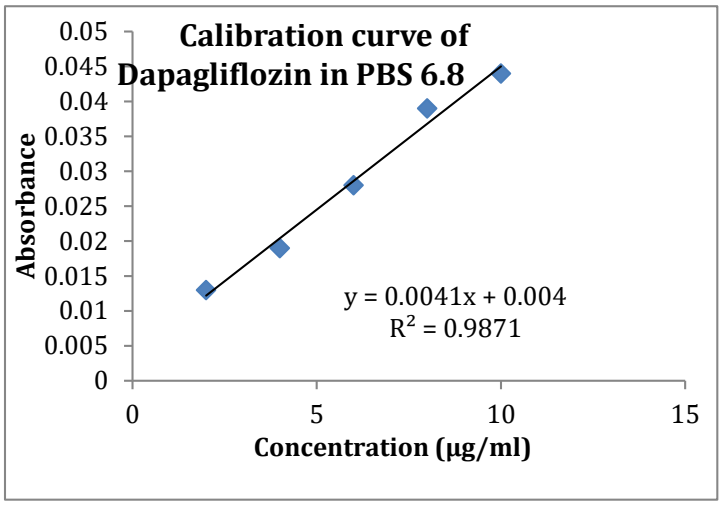

fig. no. 5: calibration curve of dapaglifozin propanediol monohydrate in phosphate buffer 6.8

Correlation Coefficient (R) = 0.9871

Equation for regression line: y = 0.0041x + 0.004 Where, X = Value of Concentration

Y = Regressed value of Absorbance 0.0041 = Slope of regressed line 0.004 = y intercept

VI. EVALUATION:

Pre Compression Parameters:

table no. 8: micromeritic properties of powder blend of core tablets formulation

Batch	*Bulk density (g/cc)*	*Tapped density (g/cc)*	*Compressibility Index (%)*	*Hausner's Ratio*	*Angle of Repose(Θ)*
C1	*0.450*	*0.550*	*14.15*	*1.19*	*25.32*
C2	*0.471*	*0.552*	*15.24*	*1.24*	*27.62*
C3	*0.421*	*0.512*	*15.44*	*1.21*	*28.50*

Post Compression parameters:

table no. 9: post compression parameters of core tablets formulation (c1 to c3)

Batch	*Weight Variation*	*Hardness (Kg/cm2)*	*Friability (%)*	*Thickness (mm)*	*Drug Content (%)*	*Disintegration Time (sec)*
C1	*150 ± 1.3*	*3.5± 0.35*	*0.94*	*3.0± 0.50*	*95.66*	*43± 1.12*
C2	*151± 1.4*	*3± 0.47*	*0.98*	*3.1± 0.22*	*96.12*	*41± 1.51*
C3	*150± 1.2*	*3.5± 0.52*	*0.92*	*3.0± 0.34*	*96.72*	*30± 0.50*

(SD ± Mean of n=3)

In Vitro Drug release of Core Tablets of Dapaglifozin:

The in vitro drug release studies of rapid release core tablets were carried out in Phosphate Buffer 6.8 for 8 hours.

table no. 10: in vitro drug release of core tablets of dapaglifozin

Time (min)	*C1*	*C2*	*C3*
5	*30.15*	*41.26*	*44.72*
10	*47.33*	*49.24*	*54.75*
15	*61.21*	*65.84*	*70.02*
20	*79.20*	*83.37*	*87.62*
30	*91.32*	*95.41*	*98.61*

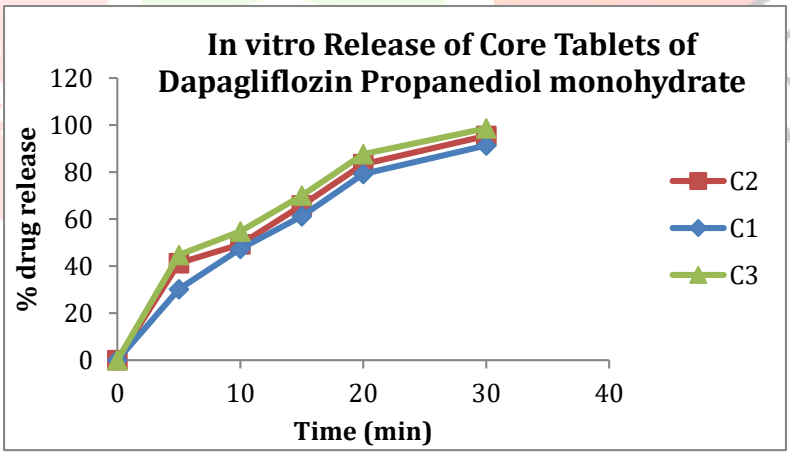

fig. no. 6: in vitro drug release profile of dapaglifozin propanediol monohydrate core tablets formulation

table no. 11: evaluation of press coated pulsatile tablets (f1 to f5)

Batch	*Weight Variation*	*Hardness (Kg/cm^2)*	*Friability (%)*	*Thickness (mm)*	*Drug Content (%)*	*Lag Time (Hr)*
F1	*351 ± 0.23*	*6 ± 0.42*	*0.62*	*4.51± 0.52*	*97.61*	*0*
F2	*353± 0.41*	*5.8 ± 0.32*	*0.51*	*4.53± 0.33*	*98.12*	*1*
F3	*351± 0.57*	*6 ± 0.57*	*0.46*	*4.50± 0.35*	*98.42*	*4*
F4	*349±0.22*	*6.2 ±0.21*	*0.52*	*4.52±47*	*97.36*	*3*
F5	*352±0.25*	*6.3 ±0.36*	*0.54*	*4.51±64*	*96.30*	*4*

(SD ± Mean of n=3)

In Vitro Drug release of Press Coated Pulsatile Tablets:

Tablets were subjected to dissolution in 6.8 pH phosphate buffer solution for subsequent hours at a temperature of 37± 0.5◦c and 50 rpm for 10 hours. The dissolution study of these formulations was performed in order to understand the effect of different polymers and their increasing concentrations. The formulation was optimized on the basis of desired value of lag time and dissolution profile. Batch F1, formulated with HPMC alone showed 0 hour of lag time and 92.63 % drug release at the end of 8 hour. Batch F2, F3 and F4 prepared with varying amount of HPMC and EC showed 91.32%, 98.6% and 88.80% drug release at the end of 8 hour respectively. Batch F5 prepared with polymer EC showed lag time of 4 hours and 35.32 % of drug release in 8 hour, high lag time and low drug release may due to hydrophobic nature of EC polymer. Among the formulations batch F3 gives sufficient lag time and optimum drug release and hence considered as optimum formulation.

The % cumulative drug release versus time data for all formulations batch is shown in table no. 6.9 and graphs has been projected in figure no. 6.9, 6.10, 6.11, 6.12, 6.13 and 6.14.

table no. 12: in vitro drug release of pulsatile tablets of dapagliflozin propanediol monohydrate

Time (Hr)	*F1*	*F2*	*F3*	*F4*	*F5*
1	*14.29*	*0*	*0*	*0*	*0*
2	*26.36*	*14.29*	*0*	*0*	*0*
3	*38.42*	*26.36*	*0*	*0*	*0*
4	*46.81*	*38.42*	*0*	*5.45*	*0*
5	*60.16*	*44.79*	*2.69*	*15.36*	*1.16*
6	*68.06*	*56.48*	*21.5*	*38.14*	*4.87*
7	*81.49*	*70.96*	*42.24*	*57.16*	*10.75*
8	*92.63*	*91.32*	*98.6*	*88.80*	*35.32*

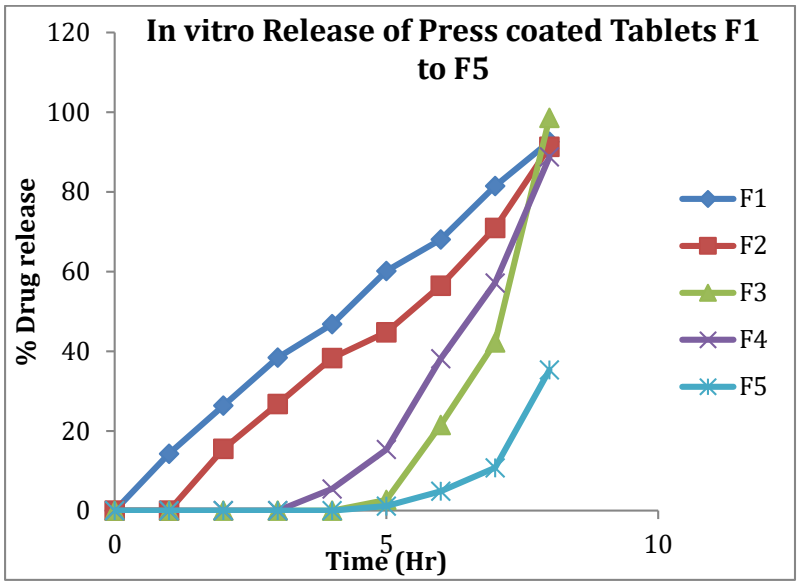

fig. no. 7: % drug release of f1 to f5

VII. CONCLUSION:

Dapaglifozin propanediol monohydrate was formulated as pulsatile tablets with different polymers. The pulsatile tablets were prepared, characterized and optimized thereafter.

Preformulation studies were performed for pulsatile tablets. The flow properties were found to be good. The physical compatibility study showed that the drug and excipients were physically compatible with each other. Chemical compatibility study using FTIR spectroscopy revealed no interaction between the drug and excipients. The in vitro release studies were performed for all the formulations of pulsatile Tablet formulation. Batch F3 showed 98.6% drug release with 4-5 Hrs lag time at the end of 8th hour. Therefore it was chosen as the optimized formulation for pulsatile drug delivery system. The accelerated stability testing was carried out for 3 months and was found to be stable.

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