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Research article *Pharmacy*

Preparation of fast dissolving oral film containing solid dispersion of carvedilol, a poorly water-soluble drug

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ABSTRACT

One of the leading causes of death and disability throughout the globe is hypertension. Ischemic or hemorrhagic stroke, myocardial infarction, heart failure, chronic renal disease, cognitive decline, and premature mortality are all increased by hypertension. Important medications for treating hypertension include carvedilol. The current treatment of hypertension with the aforementioned drugs has a number of drawbacks, according to a literature review, including a slow onset of action, extensive first pass metabolism, a high dosage regimen, poor bioavailability, and patient incompliance due to side effects like dysphasia. In order to get around these problems, we created and tested fast-dissolving oral films of solid dispersion of drug Carvedilol for oral buccal delivery.

Keywords: Hypertension, solid dispersions, fast dissolving oral films, FTIR, croscarmellose.

INTRODUCTION

Hypertension is a major contributor to the estimated 17 million annual deaths caused by cardiovascular disease (CVD) globally. Minimum 45% of fatalities from heart disease and 51% of deaths from stroke may be attributed to high blood pressure (BP), often known as hypertension. Population increase, aging, and behavioral risk factors such bad nutrition, hazardous use of alcohol, lack of physical exercise, excess weight, and exposure to chronic stress are all contributing to the rise in hypertension prevalence. Tobacco use, obesity, high cholesterol, and type 2 diabetes mellitus are additional health risks.

There are several pathophysiological disorders linked to hypertension. Causes of cardiovascular disease include ventricular hypertrophy, endothelial dysfunction, metabolic syndrome, oxidative stress, inflammation, and hereditary susceptibility. Tackling risk factors including smoking, dyslipidemia, and diabetes mellitus may help bring hypertension under control. This highlights the need for antihypertensive medicines that do more than only decrease blood pressure (BP), and instead provide benefits in the prevention and treatment of cardiovascular disease (CVD).[1]

The aforementioned antihypertensive medications represent a wide variety of Biopharmaceutical Classification classes. Some medicines in Biopharmaceutical Classification classes II and IV have poor water solubility, limiting their potential in the biopharmaceutical field. Drugs from Biopharmaceutical Classification class-II Carvedilol was chosen for this investigation. The following problems were also seen with the oral administration of these drugs:

- Poor bioavailability.
- Slow onset of action.
- Extensive first pass metabolism.
- Problem in swallowing (dysphasia) with tablet and capsule form.
- High dose and dosage regimen.

Poorly water soluble medicines have proven challenging to administer orally because of inadequate drug dissolution for gastrointestinal tract absorption. It is possible to increase a drug's bioavailability by the use of various formulation and chemical approaches.

The bioavailability of a medication may be increased by a number of chemical methods, including salt production and

the creation of a prodrug. In addition, as the medication is an NCE, conducting clinical studies for these formulations offers a significant challenge. Preparation of SDP is preferable to other methods for increasing drug solubility since it is more practical and straight forward to create.

Since SDPs result in solid oral dose forms rather than liquid as do solubilization solutions, they are more patient-friendly. SDP formulations may be made by melting the medication and dissolving it in a carrier polymer to circumvent the problems caused by the drug's insolubility in water. [2-3]

For weakly water soluble drugs, the rate limiting stages for absorption rate and extent are often drug solubility and the rate at which this solubility is acquired (drug dissolution). The bioavailability of a poorly soluble medicine may be improved by increasing its dissolving rate if the drug candidate has adequate permeability.

Solubility of drug plays major role in the process of formulation development. Solubility is the amount of solute that goes in to the solvent to form solution at given conditions of temperature, pressure and pH. Low aqueous solubility is the major problem associated with poorly water-soluble drugs. Water is always the solvent of choice for liquid pharmaceuticals formulations. Most of the drugs are weakly acidic or weakly basic with poor aqueous solubility. About 40% of the drugs from newly developed chemical entities currently being discovered are poorly water soluble. The biopharmaceutical classification system of drugs suggests low water solubility, poor dissolution, and low bioavailability of Class II and IV drugs.

Nowadays, novel fast dissolving oral films (FDF) have come in existence as an alternative dosage form in comparison with tablet, capsules, syrup and other oral dosage forms with respect to patient convenience and compliance. Fast dissolving oral films are helpful to paediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. The FDF drug delivery systems are solid dosage form which disintegrate or dissolve within seconds when placed in the mouth cavity without need of water or chewing. FDF provide better drug dissolution, faster onset of action, bypassing the first pass metabolism of drugs and thus enhance their oral bioavailability with reduced dosing frequency. These formulations are suitable for cough, cold, sore throat, allergenic conditions, nausea, pain, hypertension and CNS disorders. The present review provides the details about the recent advancement in design and development of oral fast dissolving film.

Poor aqueous solubility of drug candidates often leads to poor absorption and bioavailability from the GIT, which presents the formulation scientists with considerable challenges when trying to deliver these drug molecules via oral route. The active drug must first dissolve in the GI fluids before it can diffuse through the GIT membranes and then reach systemic circulation for drug absorption. Designing of fast dissolving oral films (FDFs) containing SDP of these poorly soluble drugs may enhance the dissolution (solubility), absorption, bioavailability by avoiding first pass effect and thus provide faster onset of action. The FDFs are seemed to be an ideal dosage form for use in especially in geriatric patients by overcoming the problem of dysphasia. FDFs may provide combined advantages of high stability of a solid dosage form and the better applicability of a liquid dosage form. The aim of the present investigation is to development and evaluation of fast dissolving oral film containing solid dispersion. To explore application of quality by design of poorly water-soluble drugs.

MATERIALS AND METHODS

List of drugs and excipients

Materials/Ingredients	Source
Acetonitrile	Loba chemie, Mumbai
Carvedilol	Gift sample from Piramal Healthcare, Indore
Citric Acid	Loba chemie, Mumbai
Croscarmellose	Signet chemicals, Mumbai
Disodium EDTA	Loba chemie, Mumbai
Ethanol	Loba chemie, Mumbai
Gelatin	Signet chemicals, Mumbai
Glycerin	S.D. Fine chemicals, Mumbai
HPMC-E5	Signet chemicals, Mumbai
HPMC-E15	Signet chemicals, Mumbai
Methanol	Loba chemie, Mumbai
Methyl cellulose	Signet chemicals, Mumbai
Microcrystalline cellulose	Signet chemicals, Mumbai
Polycarbonate filters (0.45µ)	Sigma Aldrich, USA
Polyethylene Glycol	Loba chemie, Mumbai
Potassium Dihydrogen Phosphate	Loba chemie, Mumbai
Propylene Glycol	Loba chemie, Mumbai
PVP-K30	Loba chemie, Mumbai
Sodium Alginate	Signet chemicals, Mumbai
Sodium Hydroxide	Loba chemie, Mumbai
Sodium Starch Glycolate	Signet chemicals, Mumbai
Sorbitol	Loba chemie, Mumbai

Sucrose	Loba chemie, Mumbai
Tween-80	Loba chemie, Mumbai

Pre formulation studies [4-5]

Melting point determination

Carvedilol melting points determined in triplicate using the capillary tube technique. A capillary tube containing the powdered drug ingredient was sealed at one end and placed in the sample holder of a melting point device (S.M. Scientific Ltd., Delhi). The melting point of the active pharmaceutical ingredient was measured.

Determination of λmax of drugs by UV spectrophotometric analysis

Carvedilol absorbance maxima (or max) measured against a blank solution in the range of 200 to 400 nm using a double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) .

Preparation of calibration plot of Carvedilol

The standard solution of Carvedilol was prepared in ethanolic distilled water (2:8) and phosphate buffer pH 3.8 separately to achieve different dilutions of 5, 10, 15, 20, and 25g/ml in standard volumetric flasks, and a calibration curve was then constructed in triplicate. Absorbance values were recorded by scanning these solutions against a blank at 237.8 nm using a twin beam UV visible spectrophotometer (UV1800, Shimadzu, Japan). The correlation coefficient was determined based on the linear association shown between 5 and 25 mg/ml.

Preparation of calibration plot of drugs in rat plasma by HPLC [6-7]

The retention times of Carvedilol in rat plasma were measured by recording their respective HPLC chromatograms using an HPLC (YL-9100, Younglin, Korea). In addition, an HPLC (YL-9100, Younglin, Korea) calibration plot was independently constructed for Carvedilol in rat plasma. The acetonitrile (HPLC grade) was used as an internal standard, and 1 ml of blank rat plasma was combined with it by vortexing for up to 5 minutes before 5 ml of isopropyl alcohol was added. To produce dilutions of 50, 100, 200, 500, 1000, and 5000 ng/ml in a standard volumetric flask, the solution was centrifuged at 5000 rpm for 10 minutes, and the supernatant was used to make standard solutions.

FTIR analysis

To investigate the potential for drug-HPMCE5 interactions, we recorded the FTIR spectra of HPMC-E5 and physical mixtures of these medications using an FTIR spectrophotometer (FTIR-84008, Shimadzu, Japan). For the purpose of sampling, 9mg of the aforementioned sample was combined with 300mg of KBr. Spectra were recorded by scanning the prepared samples from 4000 to 400cm-1 and then analyzing them for compatibility.

DSC Analysis

We recorded DSC thermograms of HPMC-E5, Carvedilol and physical mixtures of drugs with HPMC-E5 at a heating rate of 10°C/minutes in the range of 3-400°C under an inert nitrogen environment at a flow rate of 40ml/minutes to determine thermal behavior, crystallinity, and the likelihood of interaction or incompatibility. Using an empty pan of the same material as a standard, DSC thermograms were acquired and analyzed.

Preparation of solid dispersions (sdps) of drugs [8-9]

Using the physical mixing and solvent evaporation approach with PVP-K30 as the hydrophilic polymeric carrier, solid dispersion (SDP) of Carvedilol was created to improve their aqueous solubility. In order to improve the medications' solubility in water, researchers explored many combinations and methods and ultimately settled on one that worked best. Using a double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at max of the respective drug, the saturation solubility of SDPs synthesized using both procedures was evaluated in phosphate buffer pH 3.8.

Preparation of SDP of drugs by physical mixing

With PVP-K30 as the hydrophilic polymeric carrier, SDP of carvedilol was produced by physical mixing at drug-to-polymer ratios of 1:1, 1:2, 3:2, and 1:4. Triturating an accurately measured quantity of the medication and PVP-K30 in a glass mortar, the resulting mixture was then strained through a No. 44 sieve. Desiccators were employed to keep the mixes fresh until they were utilized in the tests.

Preparation of SDP of drugs by solvent evaporation method [10-11]

PVP-K30 was used as the hydrophilic polymeric carrier in preparation of the SDPs of carvedilol at drug-to-polymer ratios of 1:1, 1:2, 3:2, and 1:4. A clear solution of the drug and PVP-K30 was obtained by dissolving the two in 10 ml of ethanol in a beaker, and the mixture was then heated at 400^0C, while being agitated constantly. After that, the solid material was sieved through a No. 44 mesh screen and put in a desiccators until it was needed for research.

Formulation of FDFs containing SDPs of drugs [12-13]

On the basis of the aforementioned research, FDF comprising Carvedilol (CdFDF) was independently manufactured utilizing the solvent casting process and chosen formulation additives. SDP of medicine (10mg equivalent), HPMC-E5 (4045% w/w), and propylene glycol (10-15% w/w of polymer) were dissolved in 10ml of distilled water for 1 hour while being continuously stirred at 800rpm on a digital magnetic stirrer (Remi, Mumbai). After that, the casting solution was mixed with the following ingredients at room temperature: croscarmellose (1% w/w), methyl cellulose (1.2%), tween-80 (2% w/w), citric acid (1% w/w), disodium EDTA (0.5%), sorbitol (2% w/w), peppermint oil (Q.S.), and indigo carmine (Q.S.). After 4 hours of stirring at 100rpm, the casting solution was clear, eliminating the need to release any trapped air bubbles. After pouring the solution into a glycerin-lubricated glass mold, the resultant film was dried slowly at room temperature. The dried films were removed from the glass mold, cut into six $2cm^2$ squares, and then kept in double-wrapped aluminium foils.

Evaluation of SDPS

FTIR analysis

To determine whether there was a problem with medication compatibility, an FTIR spectrophotometer (FTIR-84008, Shimadzu, Japan) was used to record the spectra of PVP-K30, SDP Carvedilol. For the purpose of sampling, 9mg of the aforementioned sample was combined with 300mg of KBr. The incompatibility of the prepared samples was investigated by recording their spectra while they were scanned from 4000 to 400cm-1.

DSC Analysis

In order to detect any incompatibility, thermal behavior, or crystallinity, DSC (DSC-60, Shimadzu, Japan) thermograms of PVP-K30, SDP of Carvedilol was recorded individually.
At a flow rate of 40 ml/min, a heating rate of 10°C/minute was utilized between 3 and 400 °C in an inert nitrogen atmosphere. Using a DSC thermogram recording and analysis system, researchers compared the melting points of sample (2-3mg) and reference standard (empty aluminium pan) mixtures.

Percent practical yield

It is computed to determine how effective the cooking procedure is. The following equation was used to calculate the percentage practical yield of SDP for pharmaceuticals synthesized through the solvent evaporation process.
Effective Yield Percentage = SDP Mass Divided by Drug and Carrier Mass Times 100

Percent drug content

Each drug's SDP was accurately weighed, and then dissolved in ethanol on its own (10mg equivalent).
Drug concentrations were calculated using the following formula, after the solutions had been filtered, diluted as needed, and scanned in a double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at the wavelength of interest.

% drug content = Practical drug content / Theoretical drug content x 100

Determination of saturation solubility [14-15]

Using the saturation solubility technique, the solubility at saturation of a subset of SDPs of medicines was measured in triplicate. To equilibrate the solutions, they were agitated mechanically for 30 minutes after each drug's excess SDP was added to 10 ml of phosphate buffer pH 3.8 in a glass vial. Each vial's contents were centrifuged for 10 minutes at 2500 rpm after 72 hours. After filtering the supernatant from each vial using a 0.45 membrane filter, the filtrate was diluted to the appropriate concentration with phosphate buffer, pH 3.8. Using a double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at the prescribed wavelength of medicines versus blank, we determined the concentration of solubilized Carvedilol in SDP form.

Percent drug dissolution study [16]

Using USP paddle type equipment and phosphate buffer pH 3.8 as dissolving medium, we conducted individual experiments on the percent drug dissolution of a subset of SDPs of pharmaceuticals. Dissolution media (300 ml) was heated to 37.0 ±0.5°C and agitated at 50rpm for up to 12 minutes before SDPs (10 mg of drug) were added. After collecting 5 ml samples at 0, 2, 4, 6, 8, 10, and 12 minutes, we replenished the dissolving media to keep the total volume constant. Drugs were measured against a blank using a double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan), and samples were filtered using a membrane filter and diluted as necessary before being analyzed.

Stability study

Carvedilol was each subjected to a 90-day stability study at 25±2°C /60±5% RH. Drug content was determined using samples taken at 0, 30, 60, and 90 days.

Evaluation of FDFS

FTIR analysis

In order to make educated guesses about the properties of the finished product, the FTIR spectra of blank FDF, CdFDF was recorded using an FTIR spectrophotometer (FTIR-84008, Shimadzu, Japan). For the purpose of sampling, 9mg (crushed film) of the aforementioned sample was combined with 300mg KBr. Spectra were collected and analyzed by scanning prepared samples from 4000 to 400cm-1 in wavelength.

DSC analysis

In order to examine the properties of the final formulation, DSC thermograms of blank FDF, CdFDF was acquired using DSC (DSC-60, Shimadzu, Japan). At a flow rate of 40 ml/min, a heating rate of 10°C/minute was utilized between 3 and 400 degrees Celsius in an inert nitrogen atmosphere. Using a DSC thermogram recording and analysis system researchers compared the melting points of sample (2-3mg) and reference standard (empty aluminium pan) mixtures.

Uniformity of mass

Twenty CdFDF were picked at random and weighed on a digital balance (Shimadzu, Japan) to get an accurate reading. Cast films were sliced into pieces of 2 centimeters squared. The mean and standard deviation were then determined based on the data.

Thickness

At five locations, including the four corners and the centre, the thickness of each type of FDF was measured independently in triplicate using a digital vernier caliper (Insize, Ahmedabad).

Percent drug content [17]

FDFs were dissolved in phosphate buffer pH 3.8 three times independently to determine their drug content as a percentage ($2cm^2$ film equalling 10mg of medication).
Drug concentrations were determined using a double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) at the wavelength of the drug of interest. Samples were filtered through a 0.45m membrane filter, diluted, and then analyzed.

Folding endurance [18-19]

By repeatedly folding one film at the same spot until it broke, the folding endurance of CdFDF were independently

determined in triplicate. Folding endurance was determined by counting the number of times a film was folded before it broke in the same spot.

Surface pH

Triplier measurements of surface pH were taken using a pH meter (MKVI, Systronics, Ahmedabad) for CdFDF. The pH of distilled water and film at their metaphase was measured after being applied on FDFs.

Percent moisture uptake

Triplicate samples of CdFDF were dried for 24 hours in a desiccator before being tested for their moisture absorption percentage. The FDFs were dried to a thickness of 2 cm^2, measured, and then stored at 75% RH for a week. Weight increases due to moisture absorption were measured as a percentage after weighing FDFs again after a week.

Percent swelling [20-21]

Triplicate samples of 2cm^2 CdFDF was weighed and placed in beakers, and then 50ml of phosphate buffer pH 3.8 was added to each sample. After 60 minutes, the FDF was taken out of the beaker and its weight gain was determined using the following equation.

% S = (Ws – Wi) / A x 100

% S is the percentage of swelling, Ws is the weight of the inflated film, and Wi is the film's starting weight at zero time.

Tensile strength

With the use of a digital tensile tester, we measured the tensile strength of CdFDF (2cm^2) in triplicate. The load or force needed to break the FDFs was determined by pulling the bottom clamp of the tensile tester at a rate of 30 inch per minute. Then, the formula for calculating tensile strength was used.

Tensile strength (N/m^2) = Load at failure x 100/ cross sectional area of the film

Percent elongation

By extending FDFs over their elastic limit, we were able to accurately measure the % elongation of CdFDF in triplicate. Then, we used the following equation to figure out the degree of elongation.

% elongation = Increase in length at breaking point (cm) / Original length (cm) × 100

In-vitro disintegration time study

Disintegration times in vitro were measured in triplicate for CdFDF. The disintegration of FDFs (2cm^2) was facilitated by placing them in 20 ml of phosphate buffer pH 3.8 on a glass petridish and gently mixing the contents. A timer was used to record how long it took for FDFs to crack or disintegrate.

In-vitro percent drug dissolution or release study

Separately, in duplicate, we tested the FDFs' % dissolution in phosphate buffer pH 3.8 (300 ml) for up to 10 minutes using a USP paddle type dissolution testing device (TDT-08L, Electrolab, Mumbai). FDFs were secured to the bottom of the tank using a metal wire so that they wouldn't float away in the dissolving media. Research was done using a stirring velocity of 50rpm and a temperature of 37 0.5°C. Additionally, 1ml aliquots were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, and 10 minutes, and 1ml of new dissolution medium was added to the vessel at each time point to keep the volume of dissolution media constant.

Drugs were measured against a blank using a double beam UV visible spectrophotometer (UV1800, Shimadzu, Japan) after being filtered through a 0.45 polycarbonate filter.

Stability study [22]

According to ICH Q1A recommendations, independent stability studies of CdFDF was conducted. Two distinct settings were used to keep FDFs for up to 6 months: 25 ±2°C /60 ±5% RH and 40± 2°C /75 ±5% RH.

Physical characteristics, including film appearance and weight, and chemical parameters, including % drug content and surface pH, were estimated from samples taken at 0-30-60-90-120-180 days.

RESULTS & DISCUSSION

Pre formulation studies

Drug melting points were measured, and they were found to be within the range of typical melting points. Maximum medication concentrations (max) were calculated by UV visible spectrophotometric analysis, yielding values of 237.1 for Carvedilol. Drug calibration curves were produced using a double beam UV visible spectrophotometer in two different solutions: ethanolic distilled water (2:8) and phosphate buffer pH 6.8.

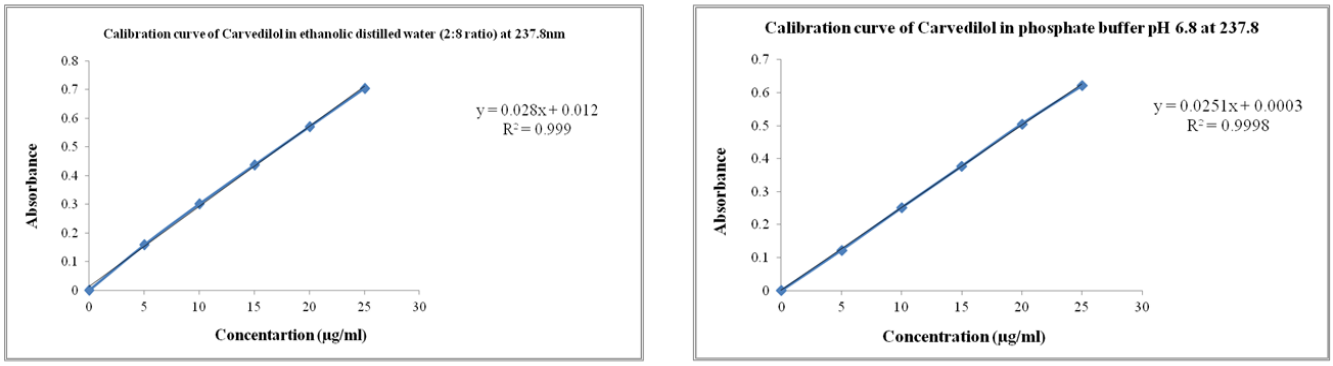


Fig 1: calibration curves of Carvedilol

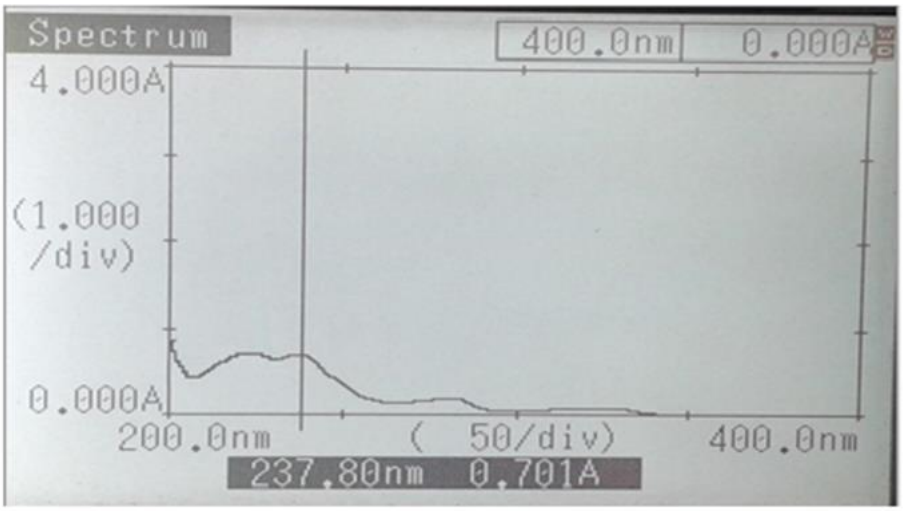


Fig 2: UV visible spectrophotometric analysis of Carvedilol

Drug retention times were calculated using HPLC chromatograms generated from rat plasma, and were reported to be 4.66 for Carvedilol. In order to determine the straight line equation and R2 values for drug's calibration plot in rat plasma, HPLC was used.

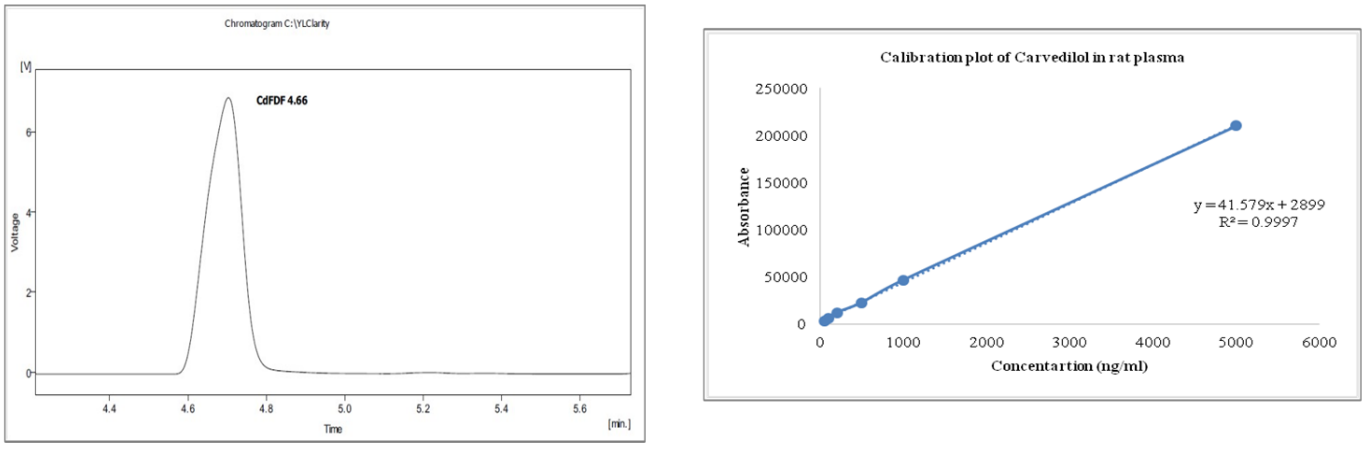


Fig 3: HPLC chromatograms analysis of Carvedilol

The findings of drug solubility investigations in various solvents showed that, in contrast to organic solvents, medicines were only slightly soluble in distilled water and phosphate buffer pH 6.8. Drug incompatibility with HPMC-E5 was determined using FTIR and DSC analysis, which showed no interaction between the two substances. It was also revealed that medication was stable between pH 4 and 8, a range in which they are often used.

FTIR analysis

Figures display the FTIR spectra of HPMC-E5, Carvedilol and physical mixtures of HPMC-E5 and HPMC-E5.

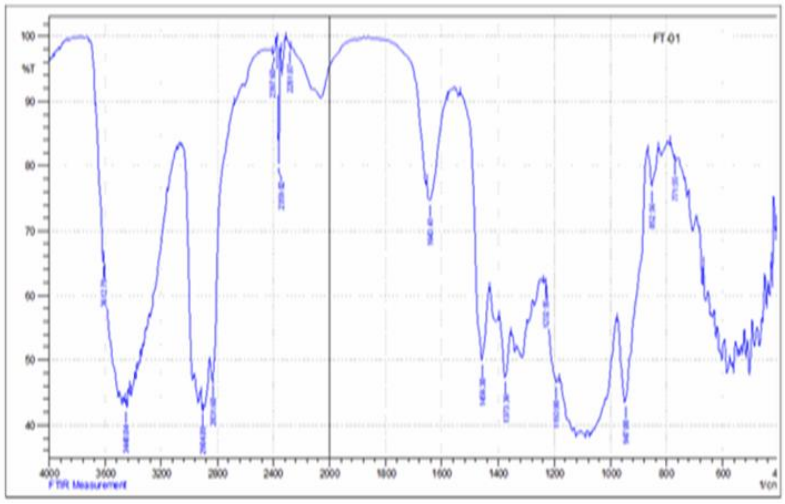


Fig 4: FTIR spectrum of HPMC-E5

The N-H stretch at 3352.59 cm-1, C-H stretch at 2904.89 cm-1, C=C stretch at 1643.41 cm-1, C-C stretch-aromatic at 1456.30 cm-1, and O-H bend at 944.08 cm-1 were the most prominent peaks in the FTIR spectra of HPMC-E5.

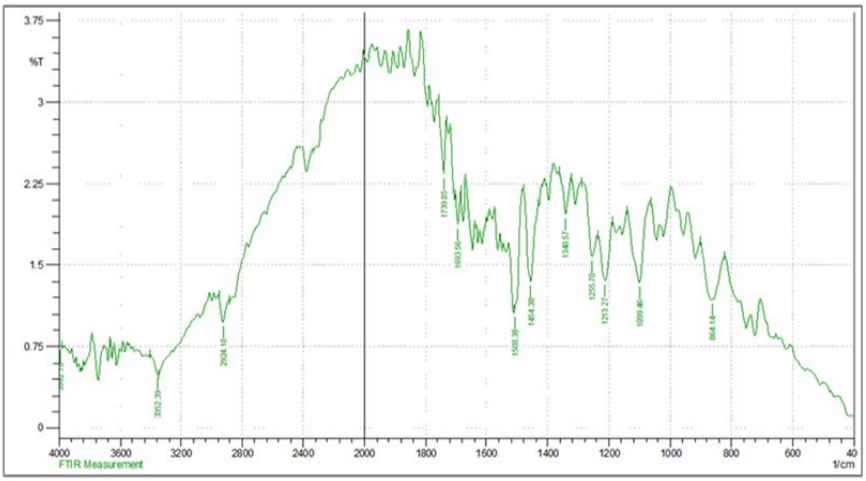


Fig 5: FTIR spectrum of Carvedilol

The N-H stretch vibrations at 3448.84cm-1, the O-H stretch vibrations at 2924.18cm-1, the C=C stretch-aromatics at 1508.38cm-1, the C-O stretch at 1255.70cm1, and the CH_2 bending at 864.14cm-1 were the most prominent peaks in the FTIR spectra of Carvedilol.

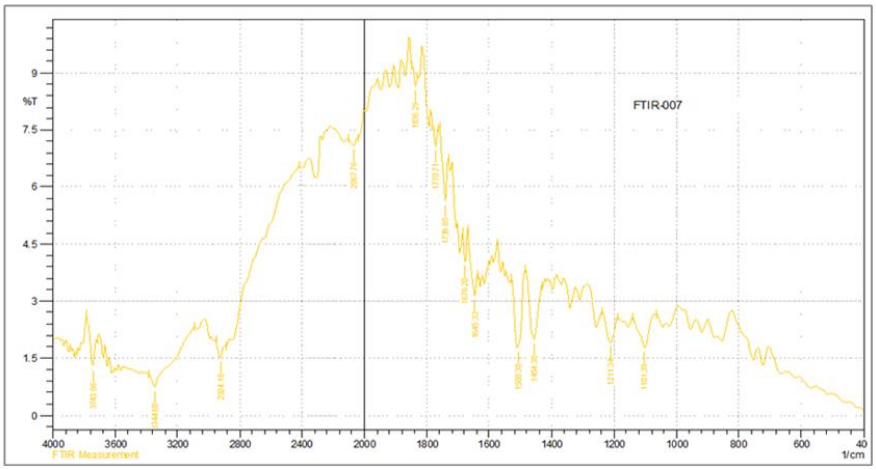


Fig 6: FTIR spectrum of physical mixture of HPMC-E5 and Carvedilol

Upon combining HPMC-E5 with Carvedilol physically, the FTIR spectra revealed prominent peaks at 3344.68cm-1 (N-H stretch), 2924.18cm-1 (O-H stretch), 1645.33cm-1 (C=C stretch), and 1456.30cm-1 (C-C stretch aromatic).

DSC Analysis

Figures show the differential scanning calorimetry (DSC) thermograms of HPMC-E5, Carvedilol as well as the physical mixtures of HPMC-E5 with each of these drugs.

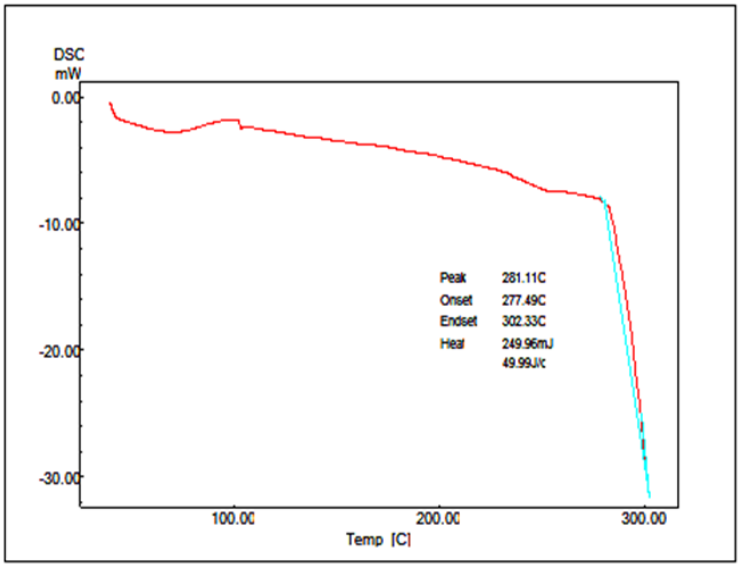


Fig 7: DSC thermogram of HPMC-E5

The melting point of HPMC-E5 was revealed by a little peak in the DSC thermogram at 281.110C. The thermogram also exhibited evidence of HPMC-E5's amorphous nature and high thermal stability.

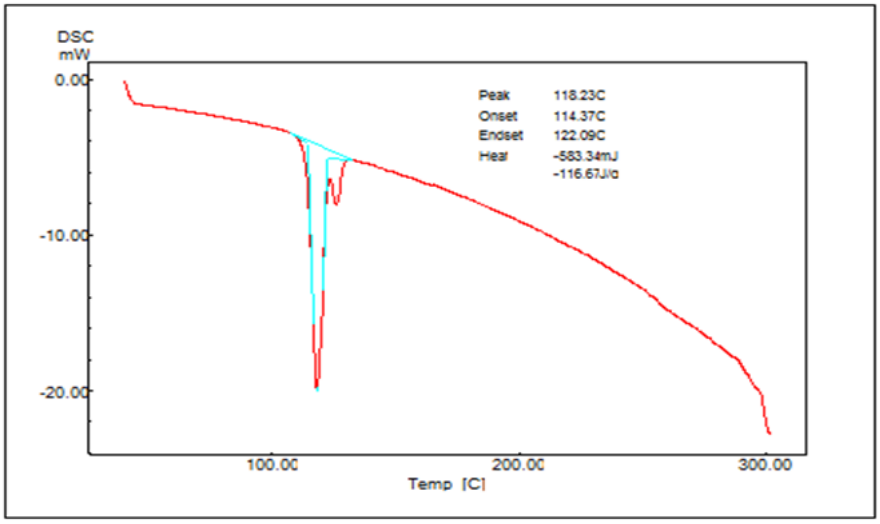


Fig 8: DSC thermogram of Carvedilol

The melting point of Carvedilol, as seen by the strong endothermic peak at 118.230C in the DSC thermogram, and the drug's extremely crystalline form were also disclosed.

Preparation of solid dispersions (SDPs) of drugs [6-7]

In order to determine the most effective technique and drug to polymer ratio for increasing solubility, PVP-K30 was used to produce SDPs of carvedilol. Based on the findings of solubility experiments, it was indicated that the drug's water solubility might be significantly improved by using SDPs made using the solvent evaporation technique with a 1:3 (drug: polymer) ratio.

Tables 1 and 2 provide the results of saturation solubility tests for Carvedilol in their respective SDPs, using either the physical mixing or solvent evaporation techniques. The results showed that a drug:polymer ratio of 1:3 compared to 1:1 and 1:2 resulted in the greatest improvement in water solubility by both approaches

Table 1: Solubility observations of SDP prepared by physical mixing (n=3)

S. No.	Drug	Polymer	Drug : Polymer ratio	Solubility in phosphate buffer pH 6.8 (Average mg/ml ± SD)
1	Carvedilol	PVP-K30	1:1	0.192 ± 0.014
2	Carvedilol	PVP-K30	1:2	0.395 ± 0.012
3	Carvedilol	PVP-K30	1:3	0.599 ± 0.011
4	Carvedilol	PVP-K30	1:4	0.601 ± 0.017

Table 2: Solubility observations of SDP prepared by solvent evaporation method (n=3)

S. No.	Drug	Polymer	Drug : Polymer ratio	Solubility in phosphate buffer pH 6.8 (Average mg/ml ± SD)
1	Carvedilol	PVP-K30	1:1	0.197 ± 0.023
2	Carvedilol	PVP-K30	1:2	0.412 ± 0.016
3	Carvedilol	PVP-K30	1:3	0.684 ± 0.015
4	Carvedilol	PVP-K30	1:4	0.689 ± 0.012

Table 3: Results of percent dissolution study of selected SDP of drugs (n=3)

S. No.	Time (minutes)	**Percent drug dissolution** (Average in % ± SD)
		Carvedilol SDP
1	0	0
2	2	34.32 ± 1.23
3	4	48.61 ± 1.46
4	6	63.78 ± 1.06
5	8	79.24 ± 1.25
6	10	91.37 ± 1.32
7	12	94.46 ± 1.74

Stability study

Results of stability studies on a subset of pharmacological SDPs. Results from periodic drug content assessment up to 90 days into the research showed no significant symptoms of instability for SDPs of any medications, indicating the excellent stability of SDPs of pharmaceuticals

.

Table 4: Data of stability studies of selected SDP of drugs (n=3)

SDP	**Percent drug content** (Average in % ± SD)			
	Initial	**After 30 days**	**After 60 days**	**After 90 days**
Carvedilol SDP	99.03 ± 0.75	98.98 ± 0.87	98.76 ± 1.05	98.64 ± 1.13

Evaluation of SDPs [8]

Various criteria were used to assess the SDP of selected medications. When comparing the FTIR spectra of SDPs to those of pure materials, the primary peaks of the drug and PVP-K30 were visible. It indicated that PVP-K30 may be used for the molecular dispersion of medicines without incompatibility for any SDPs. Crystalline endothermic peaks of medicines were less prominent in DSC thermograms of SDPs compared to those of pure samples. Drugs' crystalline behavior was found to be significantly attenuated, revealing a molecular dispersion form in the hydrophilic polymeric matrix of PVP-K30.

For a subset of SDPs, the solvent evaporation approach was shown to be very effective, yielding percentages of practical yield and drug content more than 98%. The saturation solubility technique was used to assess the solubility of SDPs in phosphate buffer at pH 6.8, and the results showed a dramatic improvement in the aqueous solubility of medicines (up to 10 times).

Dissolution rates of SDPs for Carvedilol (97.46) were measured in phosphate buffer, pH 6.8, for up to 12 minutes. Separate 90-day stability studies were conducted by assessing drug content for SDPs of carvedilol at 25± 2°C /60±5% RH. The stability analysis revealed that there were no major warning indicators of instability in SDPs for up to 90 days. It indicated that drug SDP was rather stable.

Formulation development of fast dissolving oral films (FDFs) [9]

Blank FDFs were prepared for preliminary research to determine the optimal characteristics, including film appearance, flexibility, mechanical strength, and disintegration time, for selecting the best suited technique of production and best acceptable formulation additives. The solvent casting technique was chosen as the most applicable one. Formulation additives such as HPMC-E5 (film forming agent), propylene glycol (plasticizer), croscarmellose (disintegrating agent), methyl cellulose (thickening agent), sorbitol (sweetening agent), tween-80 (solubilizing agent), citric acid (saliva stimulating agent), disodium EDTA (preservative), peppermint oil (flavoring agent) and indigo carmine (coloring agent) was found to be best suitable in

comparison with others. Separately, we used the solvent casting process and chose formulation additives to create FDFs comprising selected SDPs of Carvedilol (CdFDF). An SDP of the drug (equivalent to 10mg of drug) and other formulation additives were dissolved in 10ml of distilled water, and the resulting casting solution was casted on a fabricated glass mold greased with glycerine. Once the films had dried, they were separated from the mold and cut into six square FDFs of $2cm^2$ with an approximate weight of 150mg.
Tensile strength (R1), disintegration time (R2), and percent drug dissolution (R3) were chosen as dependent or response variables, and the concentrations of (A) HPMC-E5 (40-45% w/w), (B) propylene glycol (10-15% of w/w polymer), and (C) croscarmellose (1-5% w/w) were chosen as three independent variables (factors). Both HPMC-E5 and propylene glycol were shown to boost the tensile strength value in experimental designs. However, the tensile strength is also affected by the ideal ratio of HPMC-E5 to propylene glycol. There was no discernible effect of croscarmellose concentration shifts on tensile strength. Higher concentrations of HPMC-E5 and propylene glycol were associated with increased FDFs mechanical strength.
As the concentrations of croscarmellose and propylene glycol were increased, the disintegration time was shortened, but the disintegration time of HPMC-E5 was lengthened. Disintegration times were not significantly lengthened when hydrophilic polymer HPMC-E5 was combined with propylene glycol. At larger concentrations of croscarmellose and propylene glycol, the FDFs quickly disintegrated.
Increasing the concentrations of propylene glycol and croscarmellose resulted in a higher percentage of medication dissolution. HPMC-E5 is hydrophilic in nature and facilitates better solubility of medicine in suitable combination with plasticizer, even at larger concentration, hence it only slightly decreased the percent drug dissolution from FDFs. It showed that larger concentrations of propylene glycol, croscarmellose, and even HPMC-E5 resulted in medication dissolution rates of more than 94% from the FDFs.
For the CdDFD formulations, the linear model provided the best fit for all three response variables (R1, R2, and R3). All FDFs were found to have R2 values more than 0.9 for tensile strength, disintegration time, and percent drug dissolution, with the difference between the adjusted and anticipated R2 value being less than 0.2. Using a linear model to move across the design space was recommended

FTIR Analysis

Figures show the FTIR spectra of PVP-K30, Carvedilol.

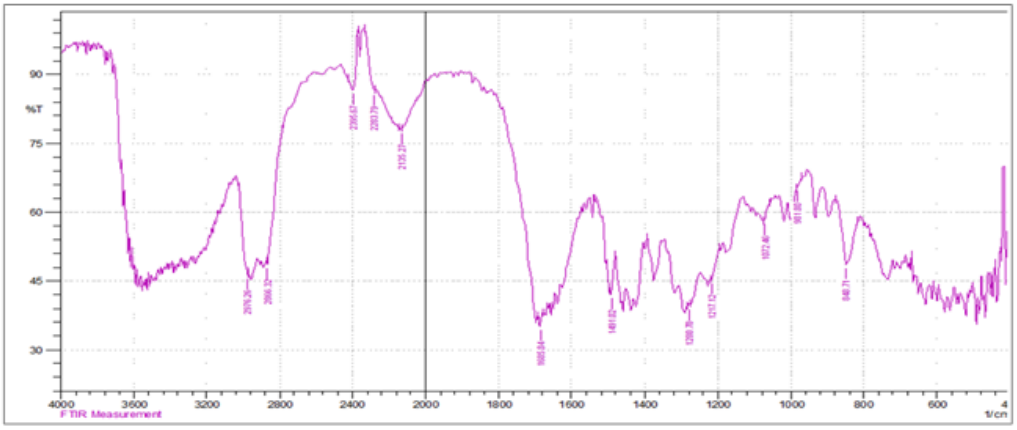


Fig 9: FTIR spectrum of PVP-K30

The C-H stretch vibration at 2976.26cm-1, the C=O stretch vibration at 1685.84cm-1, the C-H bending at 1280.78cm-1, and the N-H bend at 848.71cm-1 were the most prominent peaks in the FTIR spectrum of PVP-K30.

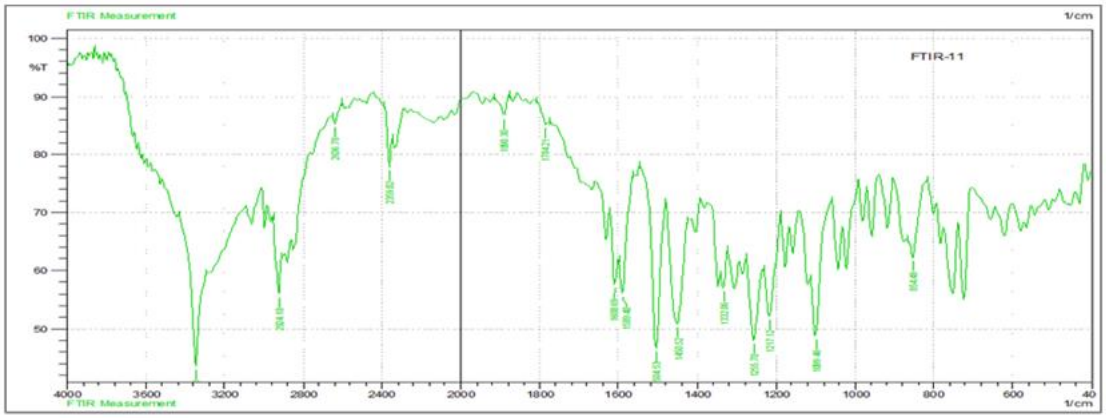


Fig 10: FTIR spectrum of SDP of Carvedilol

Carvedilol's SDP FTIR spectra has prominent peaks at 3352.84cm-1 (N-H stretch), 2924.18cm-1 (O-H stretch), 1589.40cm-1 (N-H bending), 1450.52cm-1 (C=C stretching), and 1099.46cm-1 (C-N stretch).

DSC Analysis

Figures show the differential scanning calorimetry (DSC) thermograms of PVP-K30, Carvedilol respectively.

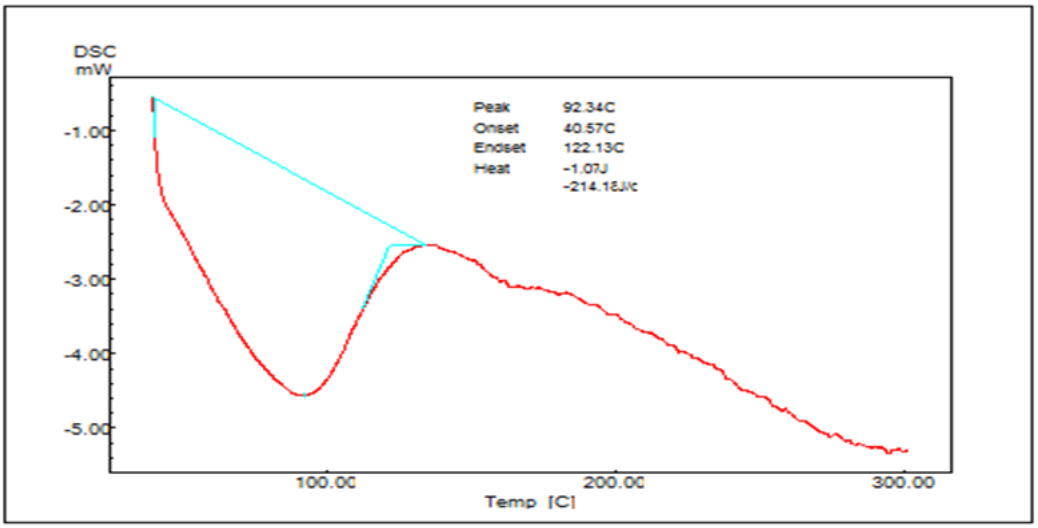


Fig 11: DSC thermogram of PVP-K30

The melting point of PVP-K30 was determined using the DSC thermogram, which also revealed that the compound is extremely amorphous due to the presence of a large endothermic peak at 92.340C.

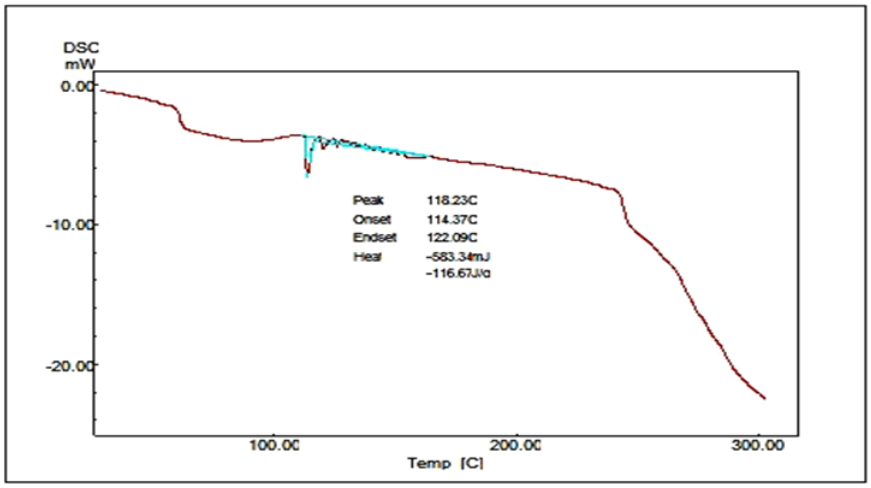


Fig 12: DSC thermogram of SDP of Carvedilol

When comparing the DSC thermogram of the SDP of Carvedilol to that of the pure drug, the endothermic peak at 118.230C is quite tiny. Thus, it demonstrated the medication was present in a molecular dispersion form with PVP-K30, indicating a decrease in Carvedilol's crystalline structure.

Percent practical yield

Table 4.25 displays the estimated data of the percent practical yield of SDP of medicines synthesized by solvent evaporation technique, showing that the yield rose with the quantity of PVP-K30. For several SDPs, it showed a yield of above 98% in practice.

Table 5: Results of percent practical yield of SDPs (n=3)

S. No.	Drug	Polymer	Drug : Polymer ratio	% Practical Yield (Average in % ± SD)
1	Carvedilol	PVP-K30	1:1	96.63 ± 1.23
2	Carvedilol	PVP-K30	1:2	94.12 ± 1.41

3	Carvedilol	PVP-K30	1:3	98.85 ± 1.03
4	Carvedilol	PVP-K30	1:4	98.89 ± 1.12

Percent drug content

Table 4.26 displays the percent drug content for a selection of SDPs of drugs, which was found to be about 99% with low standard deviation. It showed that all medication SDPs had the same information.

Table 6: Results of percent drug content of selected SDPs (n=3)

S. No.	Drug	Polymer	Drug : Polymer ratio	% Drug Content (Average in % ± SD)
1	Carvedilol	PVP-K30	1:3	99.03 ± 0.75

Determination of saturation solubility

Table displays the saturation solubility of various SDPs of medicines. The research found that the water solubility of pharmaceuticals in their SDP form was around 10 times higher compared to pure medications, and that the crystallinity of drugs in molecular dispersion form with PVP-K30 was reduced.

Table 7: Results of saturation solubility study of selected SDPs (n=3)

S. No.	Drug	Polymer	Drug : Polymer ratio	Solubility in phosphate buffer pH 6.8 (mg/ml ± SD)
1	Carvedilol	PVP-K30	1:3	0.684 ± 0.015

Percent drug dissolution study

Table and Figure provide the % drug dissolving data for certain SDPs of medicines. Carvedilol was all reported to have a % drug dissolution of SDP of 94.46%, respectively. It indicated that medicines in SDP forms might dissolve virtually entirely within 12 minutes.

Table 8: Results of percent dissolution study of selected SDP of drugs (n=3)

S. No.	Time (minutes)	Percent drug dissolution (Average in % ± SD)
		Carvedilol SDP
1	0	0
2	2	34.32 ± 1.23
3	4	48.61 ± 1.46
4	6	63.78 ± 1.06
5	8	79.24 ± 1.25
6	10	91.37 ± 1.32
7	12	94.46 ± 1.74

Stability study

Table displays the results of stability studies on a subset of pharmacological SDPs. Results from periodic drug content assessment up to 90 days into the research showed no significant symptoms of instability for SDPs of any medications, indicating the excellent stability of SDPs of pharmaceuticals.

Table 9: Data of stability studies of selected SDP of drugs (n=3)

SDP	Percent drug content (Average in % ± SD)			
	Initial	After 30 days	After 60 days	After 90 days
Carvedilol SDP	99.03 ± 0.75	98.98 ± 0.87	98.76 ± 1.05	98.64 ± 1.13

Evaluation of FDFs

Parameters were compared for CdFDF formulations. When comparing the FTIR spectra of pure materials to those of FDFs, the primary peaks of the medications were clearly visible. In the end, the FDF formulations showed no symptoms of incompatibility. The DSC thermograms of FDFs demonstrated the medications molecular dispersion form and the reduction in crystallinity of FDFs.

In-vitro disintegration time studies on FDFs showed that they disintegrated quickly, suggesting that they might help speed up medication dissolution. Disintegration time was similarly reduced when croscarmellose and propylene glycol concentrations were increased. Optimised and verified FDFs showed more than 95% drug dissolve up to 10 minutes in in-vitro percent drug dissolution or release experiments, indicating quicker and virtually full drug dissolution. Higher concentrations of propylene glycol and croscarmellose led to a greater percentage of medication dissolution.

Separate tests were conducted to evaluate the physical and chemical stability of CdFDF up to 6 months in accordance

with ICH Q1A recommendations. All FDFs were more stable when kept at 25±2°C /60±5% RH than when kept at 40±2°C /75±5% RH.

Maximum absorption of Carvedilol from oral suspension was determined to be 225.37± 0.055, g/ml up to more than 3 hours respectively, based on an in-vivo pharmacokinetic study. While CdFDF had maximal drug absorption rates of 565.01±0.059 g/ml up to 1 to 2 hours, respectively, when administered through the buccal cavity. The research found that, in contrast to oral solution, FDFs are rapidly absorbed by the body via the buccal canal, and their bioavailability is increased by avoiding first pass metabolism by up to over 90%.

FTIR analysis

Figures show the FTIR spectra of blank FDF, CdFDF respectively

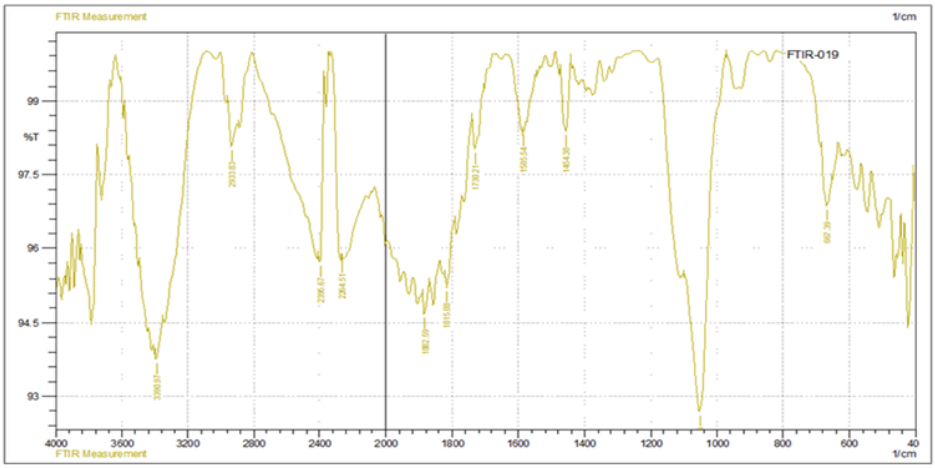


Fig 13: Spectrum of blank FDF

The O-H stretch at 3390.97cm-1, the C-H stretch of alkanes at 2933.83cm-1, the C-C aromatic stretch at 1454.38cm-1, and the C-C aliphatic stretch at 1119.7cm-1 were the most prominent peaks in the FTIR spectra of blank FDF.

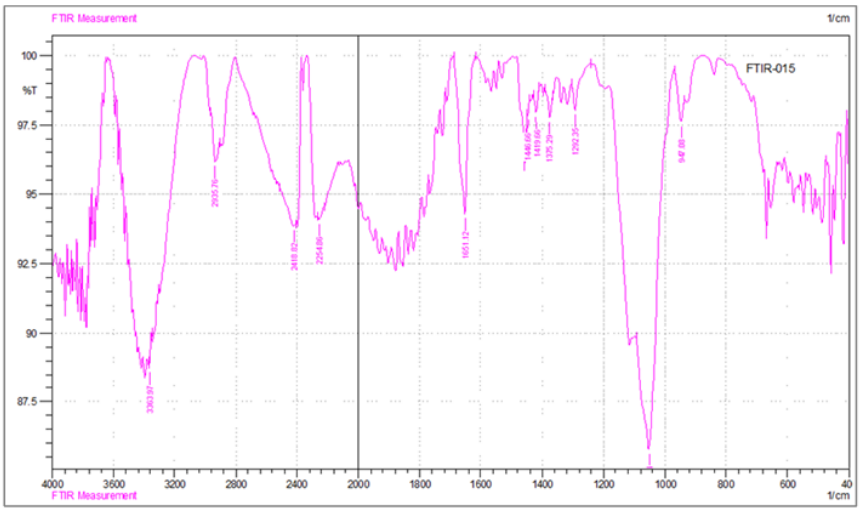


Fig 14: FTIR spectrum of CdFDF

N-H stretching at 3363.97 cm-1, C-H stretching at 2935.78 cm-1 (alkanes), C=C stretching at 1651.12 cm-1, C=C stretching at 1446.66 cm-1 (aromatic), and O-H bending at 944.08 cm-1 were the most prominent peaks in the FTIR spectra of CdFDF.

DSC analysis

Thermogravimetric (DSC) profiles of blank FDF, CdFDF are shown in

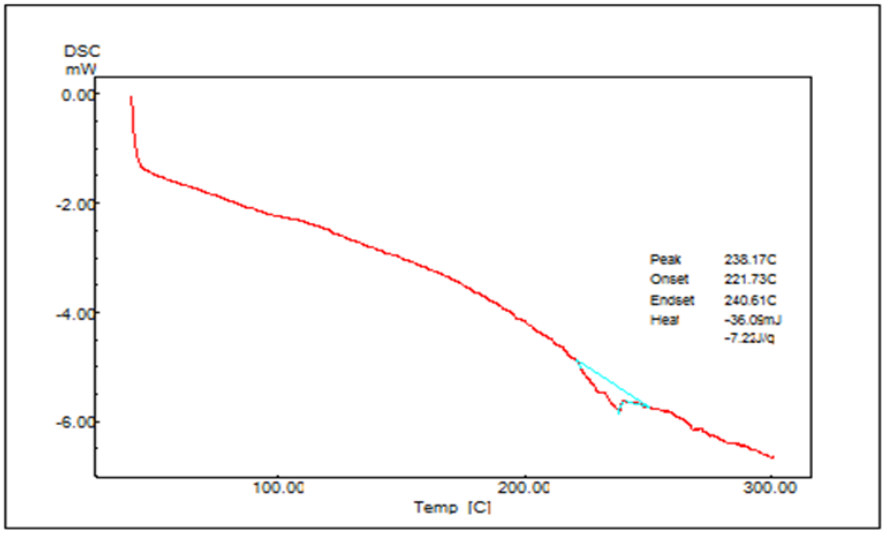


Fig 15: DSC thermogram of blank FDF

One endothermic peak at 238.10C was seen in the DSC thermogram of HPMC-E5 blank FDF, showing the melting temperature of HPMC-E5, which was found to be marginally inhibited when the material was in the form of film.

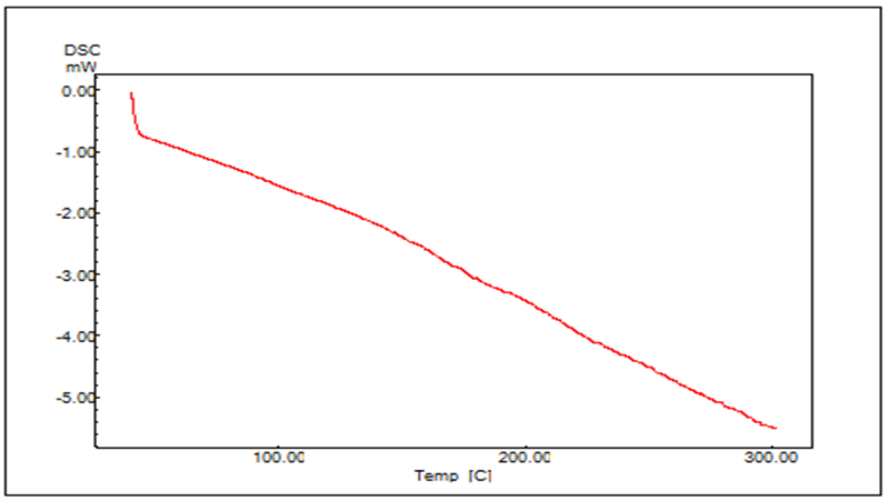


Fig 16: DSC thermogram of CdFDF

There was no indication of Carvedilol in molecular dispersion form in the film formulation as evidenced by the DSC thermogram of CdFDF. This result demonstrated that Carvedilol was successful in reducing its crystalline behavior.

Uniformity of mass

CdFDF averaged 146.25±0.87 mg, respectively, after optimization and validation. It was determined that the mass of the spliced footage from various locations was the same.

Thickness

The thickness of the optimized and verified FDFs was determined to be 0.243 ±0.011mm for CdFDF. The thickness of FDFs was shown to grow with increasing HPMC-E5 and propylene glycol concentrations. Film samples taken from a variety of locations were all measured to have the same thickness.

Percent drug content

CdFDF was all determined to have a drug content of 99.31 ±0.74%, respectively, after optimization and validation. The data as a whole showed a high degree of content homogeneity among FDFs.

Folding endurance

The results indicated that a higher concentration of HPMC-E5 and propylene glycol was beneficial to folding endurance.

Surface pH

The surface pH of the CdFDF, was improved and verified was determined to be 6.78 ±0.03. The research found that the FDFs had a pH that was very close to neutral, meaning that there was very little likelihood that they would irritate the oral mucosa after being taken orally.

Percent moisture uptake

CdFDF was all found to absorb moisture at a rate of 2.03 ± 0.02%, respectively, after undergoing optimization and validation. The research found that the moisture absorption improved with increasing propylene glycol content. It also hinted that the FDFs exhibited some modest hygroscopic activity when exposed to high humidity.

Percent swelling

Swelling percentages for optimized and verified FDFs ranged from 41.27 ±0.31 percent for CdFDF. Increased drug absorption from a phosphate buffer at pH 6.8 and a higher swelling percentage of FDFs showed its feasibility for fast drug release.

Tensile strength

The optimized and verified CdFDF has tensile strengths of 0.212± 0.005 N/m^2. When the concentrations of HPMC-E5 and propylene glycol were increased, the tensile strength values increased significantly. It also showed that FDFs have high mechanical strength and are resistant to cracking and rupturing.

Percent elongation

After optimization and validation, the percent elongation of CdFDF 14.51±1.02. Increases in HPMC-E5 and propylene glycol content were associated with increases in the mechanical strength of FDFs.

In-vitro disintegration time study

Disintegration time values of FDFs determined in vitro are shown in table. The optimized and certified FDFs had a disintegration time of 23.73 ± 0.26 seconds for CdFDF.
Disintegration times were found to be significantly reduced when croscarmellose and propylene glycol concentrations were increased. It demonstrated the rapid decomposition of FDFs and permitted the expedited release of medicines.

In-vitro percent drug dissolution or release study

The results of in-vitro experiments that measured the percentage of medication breakdown or release from FDFs. CdFDF was improved and confirmed to have percent drug dissolution values of 96.57±0.60 respectively. Table display results of in-vitro % dissolution or release experiments for optimized and validated FDFs.
The results revealed that when the concentrations of propylene glycol and croscarmellose were increased, the percentage of medication dissolution also rose significantly. It showed that more than 95% of the medication was dissolved up to 10 minutes, indicating a quicker and almost full drug breakdown.

Stability study

Six-month stability statistics for optimized and verified CdFDF is shown in tables 4. Physical appearance, film weight, percentage of drug content, and surface pH were all seen to be stable up to six months under both storage settings. When compared to FDFs held at 40 ± 2°C/75± 5% RH, FDFs stored at 25 ± 2°C/60 ± 5% RH showed greater stability.

Table 10: Stability study data of CdFDF (n=3)

	Storage at 25 ± 2°C/60 ± 5% RH for 6 months			
Days	**Appearance**	**Weight** (Avg. mg ± SD)	**Drug content** (Avg. % ± SD)	**Surface pH** (Avg. pH ± SD)
0	Transparent	146.25 ± 0.87	99.31 ± 0.74	6.78 ± 0.03
30	No Change	146.21 ± 0.93	99.28 ± 0.31	6.78 ± 0.02
60	No Change	146.10 ± 0.85	99.19 ± 0.38	6.78 ± 0.03
90	No Change	146.06 ± 1.04	99.17 ± 0.19	6.77 ± 0.02
120	No Change	146.03 ± 0.99	99.15 ± 0.24	6.76 ± 0.02
180	No Change	146.01 ± 0.87	99.11 ± 0.36	6.76 ± 0.03
	Storage at 40 ± 2°C/75 ± 5% RH for 6 months			
0	Transparent	146.25 ± 0.87	99.31 ± 0.74	6.78 ± 0.03
30	No Change	146.13 ± 0.84	99.26 ± 0.23	6.78 ± 0.01
60	No Change	146.06 ± 0.76	99.15 ± 0.15	6.76 ± 0.01
90	No Change	145.97 ± 0.91	99.05 ± 0.31	6.74 ± 0.02
120	No Change	145.94 ± 0.95	99.01 ± 0.37	6.74 ± 0.01
180	No Change	145.89 ± 0.92	98.98 ± 0.18	6.73 ± 0.02

CONCLUSION

The aqueous solubility of Carvedilol was significantly improved during SDP preparation utilizing the solvent evaporation technique with PVP-K30 up to 1:3 (drug to polymer ratio). The optimized and verified FDFs evaluated showed promising results across a range of properties, including mechanical strength, content homogeneity, surface pH, disintegration time, drug dissolution/release efficiency, and stability for up to six months. Due to the elimination of first pass metabolism, medicines in FDF was absorbed more quickly and had greater oral bioavailability up to 1 to 2 hours after buccal injection. Because of their rapid onset of action, lack of first-pass metabolism, low dosage regimen, increased bioavailability (up to 2-3 fold), and increased patient compliance, it follows that CdFDF could be commercially exploited for the treatment of hypertension.

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