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FORMULATION AND EVALUATION OF CARVEDILOL PHOSPHATE EXTENDED RELEASE TABLETS ALONG WITH AUTO DOCKING ANALYSIS, PREDICTIONS OF PHARMACOKINETICS AND DRUG-LIKENESS PROPERTIES STUDIES

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ABSTRACT

Introduction: Carvedilol phosphate, a non-selective beta-blocker, is used for the treatment of hypertension and heart failure. Extended-release formulations enhance therapeutic efficacy and patient compliance by ensuring prolonged drug release. **Aim:** This study focuses on the formulation and evaluation of extended-release carvedilol phosphate tablets, including pre-compression and post-compression analysis, in vitro drug release, molecular docking studies, pharmacokinetic predictions, and drug-likeness evaluation. **Methods:** Extended-release tablets were prepared using hydroxypropyl methylcellulose (HPMC K4M and K100M) via the wet granulation method. Pre-compression parameters such as identification, determination of powder characteristics like tapped density, untapped density, angle of repose, and loss on drying were assessed. Post-compression studies included average weight, group weight, uniformity of weight variation, thickness, hardness, friability, dissolution studies, related substances, and assay using HPLC. Molecular docking (AutoDock) analyzed carvedilol's binding affinity to beta-adrenergic receptors, while SwissADME predicted pharmacokinetic properties and drug-likeness. **Results:** All

formulations met pharmacopoeial standards for weight uniformity, thickness, and friability. Formulations F2 and F7 exhibited higher hardness. Dissolution studies confirmed extended drug release over 20 hours. Docking studies revealed strong receptor binding, suggesting effective targeting. Pharmacokinetic analysis showed moderate solubility, low bioavailability (0.17), and a favorable metabolic profile. Drug-likeness evaluation indicated compliance with Lipinski's rule of five, confirming its potential as an oral therapeutic agent. **Conclusion:** This study successfully developed extended-release carvedilol phosphate tablets with desirable physicochemical properties. Computational studies supported the formulation's potential for improved therapeutic outcomes.

KEYWORDS: Carvedilol Phosphate, Extended-Release Tablets, Molecular Docking, Pharmacokinetics, Drug-Likeness Properties.

1. INTRODUCTION[1-4]

The oral route remains the most commonly preferred method for drug administration, primarily due to its ease of use and the gastrointestinal tract's adaptability in dosage form design. Various terminologies, such as sustained release, prolonged release, modified release, extended release, or depot formulations, are used to describe drug delivery systems designed to maintain therapeutic drug levels by gradually releasing the medication over an extended period following a single dose. Extended-release dosage forms offer at least a twofold reduction in dosing frequency compared to conventional formulations. Carvedilol phosphate, a non-selective β-blocker classified under BCS Class II, is widely used in the treatment of hypertension. However, it exhibits low solubility and limited bioavailability, posing challenges in its formulation and therapeutic effectiveness.

The molecular docking studies of Carvedilol phosphate provide insights into its binding interactions with target proteins, which is crucial for understanding its mechanism of action at the molecular level. The bioactivity of Carvedilol phosphate was predicted using the RCSB Protein Data Bank (PDB), a comprehensive repository of protein structures that facilitates molecular docking and interaction studies. Pharmacokinetics and drug-likeness studies play a vital role in drug development by assessing the absorption, distribution, metabolism, and excretion (ADME) properties. SwissADME, an online tool, was used to evaluate the lipophilicity, solubility, and pharmacokinetic parameters of Carvedilol phosphate. These studies help in predicting the drug's oral bioavailability and potential success in clinical applications.

2. MATERIALS AND METHODS[5-14]

2.1. Materials

The formulation consists of various ingredients sourced from different vendors. Carvedilol phosphate (API) was obtained from Symed Labs Limited, while Hydroxypropyl methylcellulose K4M, acting as a polymer and suspending agent, was supplied by Taianruital. Lactose DCL 11, serving as a binder and wetting agent, was procured from DFE Pharma, and Microcrystalline cellulose 102, used as a diluent and binder, came from Sigachi. Polyplasdone K90 (PVPK90), functioning as a binder and stabilizing agent, was sourced from Ashland, whereas Quinoline yellow lake, a colorant, was obtained from Neelikon. Starch, a disintegrant, was provided by Universal. The binder preparation included Povidone K30 from Ashland and Isopropyl alcohol from Deepak as a solvent. In the lubrication step, Colloidal silicon dioxide, serving as an absorbent and glidant, was procured from Cabot Sanmar. Talc, a lubricant, was obtained from Neelkanth, while Magnesium stearate, another lubricant, was supplied by Nitika Pharmaceutical. Finally, Hydroxypropyl methylcellulose K100M, used as an extended enhancer and for improving flow properties, was also sourced from Taianruital. The total average weight of each formulation was 155 mg.

2.2. Instruments

The study involved the use of various instruments sourced from different manufacturers. The Fourier Transform Infrared Spectrophotometer was obtained from Perkin Elmer Spectrum RX 1, while the UV-Visible Spectrophotometer was supplied by Jasco. A Single Pan Digital Balance from Shimadzu BL220H was used for precise weighing. The Digital pH Meter, sourced from Hanna Instruments, Italy (HI98), was employed for pH measurements. Eltek MS 2012 Magnetic Stirrer facilitated sample mixing, while Bandelin Sono Plus Model HD 2070 Sonicator was used for sonication. The Freeze Drier was supplied by Labconico, USA, and the Research Centrifuge was from Hitachi Centrifuge, USA. For chromatography analysis, a High-Performance Liquid Chromatograph (HPLC) from Shimadzu was utilized. Additional equipment included a Magnetic Stirrer from Remi, a Compression Machine from Cadmach, and a Dissolution Apparatus from Lab India, ensuring accurate and efficient formulation studies.

2.3 In Silico Studies

Softwares and Databases used

Accerlys discovery studio viewer, Smile Translator(Online), RCSB protein data bank, Autodock 4.2 which combines, Autodock tools, Python molecule viewer 1.5.6, Vision 1.5.6.

2.4 Evaluation of pre compression studies

2.4.1 Granulation

Extended-release tablets were prepared using hydroxypropyl methylcellulose (HPMC K4M and K100M) via the wet granulation method.

Fig. 1: Extended-release carvedilol phosphate tablets.

2.4.2 Identification of drug

The colour, odour, and appearance of the drug sample were evaluated as part of the organoleptic properties assessment in the pure drug study.

2.4.3 Determination of Powder Charactertics

a. Density

The bulk density was determined by gently pouring the powders into a 100 ml volumetric cylinder up to a total volume of 90 ml. After weighing the above volume of powder, the bulk density was determined using equation as presented below.

Density = Weight (gm)/Volume (ml)

For the measurement of tap density, the cylinder was tapped over a 0.5 inch vertical drop, using a tap density tester, until a constant volume was observed.

b. Angle of Repose

The angle of repose (θ) for each powder was determined by placing the powder in a funnel with the following critical dimensions: Orifice diameter 10 mm and base diameter 65 mm. The tip of the orifice of the funnel was at fixed height from the ground horizontal surface, and the powder was allowed to flow only under the force of gravity.

The angle of repose, θ was calculated from the following relationship.

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

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

(Where h is height of the pile of powder and r is the radius of the base of cone).

2.4.4 Loss on Drying

After drying is completed, open the drying oven, close the bottle promptly and allow it to cool on room temperature (where applicable) in a desiccator. Weigh the Bottle and note down the weight of sample.

LOD calculated from the following relationship

$$\% \text{ of LOD} = \frac{Weight\ loss}{Weight\ of\ sample} \text{ X } 100$$

Where,

Weight of the sample = (B-A) mg

Weight loss = (B-C) mg

2.5Evaluation of post-compression Studies

2.5.1 Appearance

Visually checks 20 -tablets were identified by checking the difference in color.

2.5.2 Identification by HPLC

Identify drugs: In the HPLC Method, the retention time is related to the structure and properties of the components, and is one of the qualitative parameters, which can be used to identify drugs.

2.5.3 Average Weight of 20-Tablets

Weighing of 20 tablets from each formulation by using Digital Weighing Balance. Measuring units of tablets is Milligram (mg).

2.5.4 Uniformity Weight variation

Weighing of 20 tablets Individually from each formulation by using Digital Weighing Balance. Measuring units of tablets is Milligram (mg).

2.5.5 Thickness

The thickness of the five-tablets was Measured using a Vernier Caliper. Measuring units of tablets is Millimeter (mm). Five tablets from each Formulation were used and mean ± Standard Deviation was calculated.

Diameter

The Diameter of the five-tablets was Measured using a Vernier Caliper. Measuring units of tablets is Millimeter (mm). Five tablets from each Formulation were used and mean ± Standard Deviation was calculated.

2.5.6 Hardness

Hardness of Tablets was measured using Monsanto tester. Measuring units of tablets is Newton (N). For each Formulation five Tablets were tested.

2.5.7 Friability

Twenty tablets (or 6.5gm) were weighed and placed in the friabilator apparatus was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were de-dusted and weighed again. The percentage friability was measured using formula,

$$\% F = W1 - W2 / W1 \times 100$$

Where, % F = Friability in percentage

W1 = Initial / Before Tumbling weight of tablets

W2 = Weight of tablets after revolution / After Tumbling /Friability

2.5.8 Dissolution

Apparatus Paddle Basket Method-Medium-900ml, 0.1N Hydrochloric Acid, RPM -100, time-1,4,8,20th Hours 37˚C ± 0.5˚C

2.5.9 Uniformity of content by HPLC

In the assay, the principle peak in the chromatogram obtained with sample solution should correspond to the peak due to carvedilol phosphate in the chromatogram obtained with standard solution.

2.5.10 Related substance by HPLC

Any individual Impurity & Total Impurity are obtained in HPLC Chromatographically method.

2.5.11 Assay by HPLC

In the assay, the principle peak in the chromatogram obtained in HPLC Chromatographically method.

2.6 Docking Studies

The bioactivity of Carvedilol Phosphate was predicted using RCSB Protein Data Bank.

2.7 Pharmacokinetics and Drug-likeness Studies

SwissADME was used to evaluate lipophilicity, solubility, and pharmacokinetic parameters.

RESULTS AND DISCUSSION

A. Evaluation of pre-compression Studies

Table 1: Evaluation Parameters of Pre-Compression Studies.

S.No	Test	Specification	Observation
1	Colour	White or off-White Crystalline powder	White or off-White Crystalline powder
2	Odour	Odourless	Odourless
3	Taste	Bitter	Bitter
4	Solubility	Sparingly soluble in water, Freely soluble in Ethanol and Methanol	Complies
5	Moisture Sensitivity	Hygroscopic	Hygroscopic
6	Melting Point	117 -122°C	120°C±1.33
7	Loss on Drying	≤ 0.5%	0.2%

B. Evaluation of post-compression Studies

Table 2: Evaluation Parameters of Post-Compression Studies.

S.No	Compress the Lubricated blend with following Parameters		Observation
1.	Description	Yellow coloured, Circular shaped, slightly bi-convexed, uncoated extended release tablet and plain on both side.	Complies
2.	Average weight	155 mg ± 2% (151.90 mg - 158.10 mg)	154mg
3.	Weight of 20 tablets	3.100 g ± 2% (3.038 g - 3.162 g)	3.088gm
4.	Uniformity of weight Average weight	± 5% (147.25 mg - 162.75 mg)	Mini. 151 mg Maxi. 158 mg
5.	Thickness	3.20 mm ± 0.3 mm (2.90 mm - 3.50 mm)	3.18mm
6.	Hardness	Target: 1OON (60 – 125 N)	94N
7.	Friability	NMT 1.0% w/w	0.12%

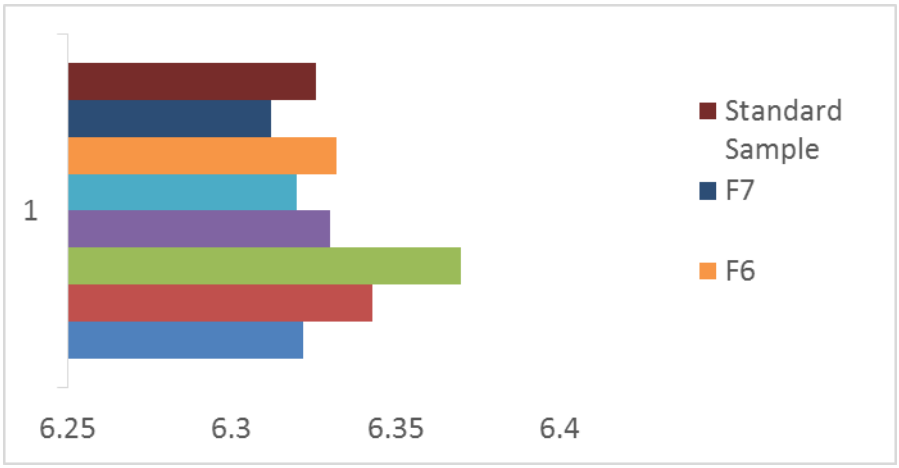


Fig. 2: Identification By Hplc of Carvedilol Phosphate Extended Release Tablets.

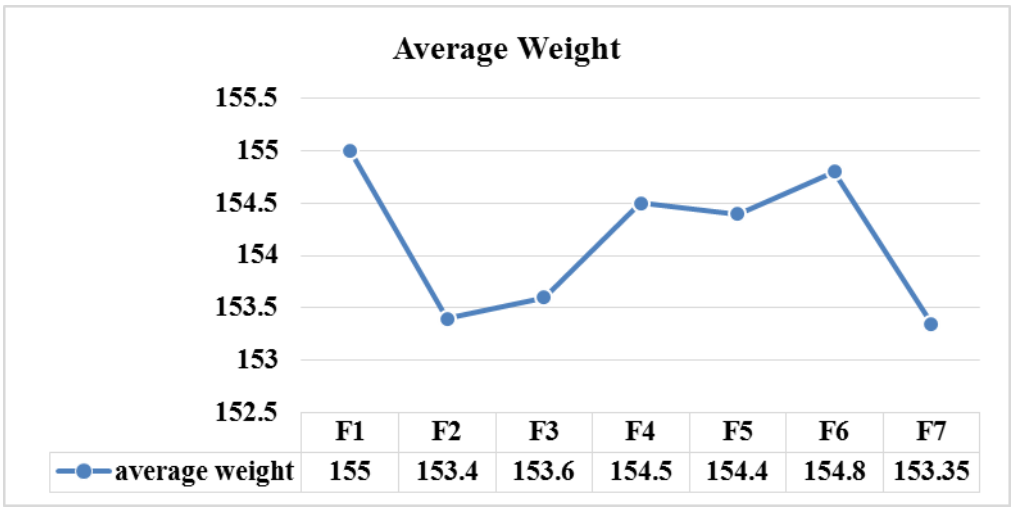


FIG. 3: Weight of 20 Tablets Of Carvedilol Phosphate Extended Release.

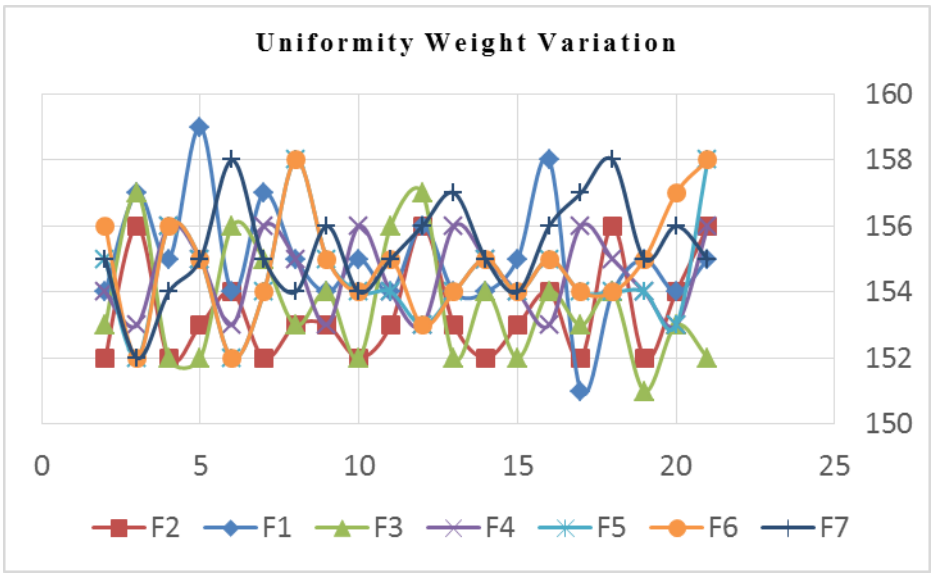


FIG. 4: Uniformity Weight Variation of Ig:- 9 Assay By Hplc Of Carvedilol Phosphate Extended Release Tablets.

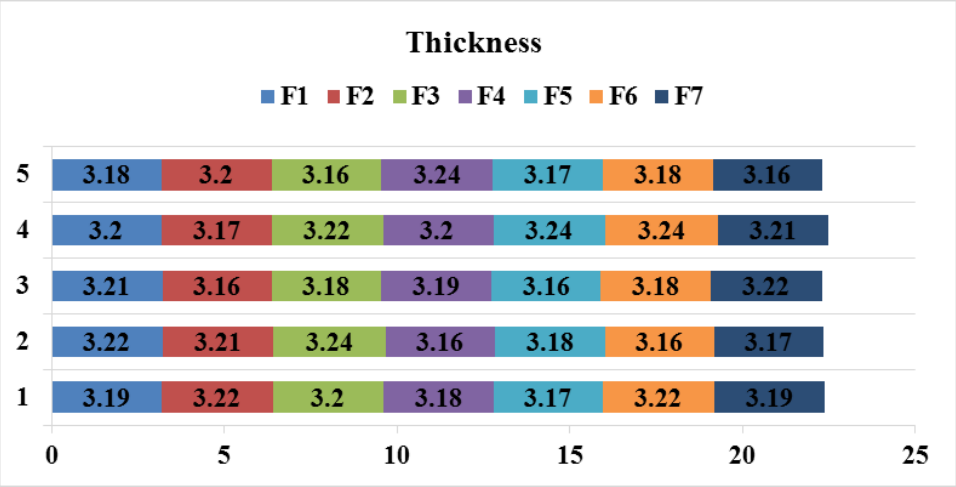


FIG:- 5: Thickness of Carvedilol Phosphate Extended Release Tablets.

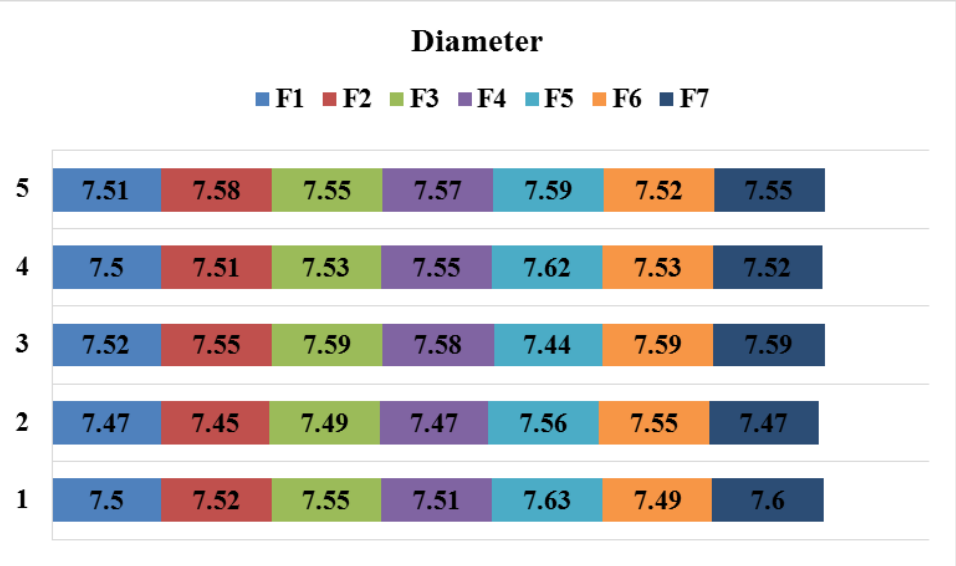


FIG:- 6 Diameter of Carvedilol Phosphate Extended Release Tablets.

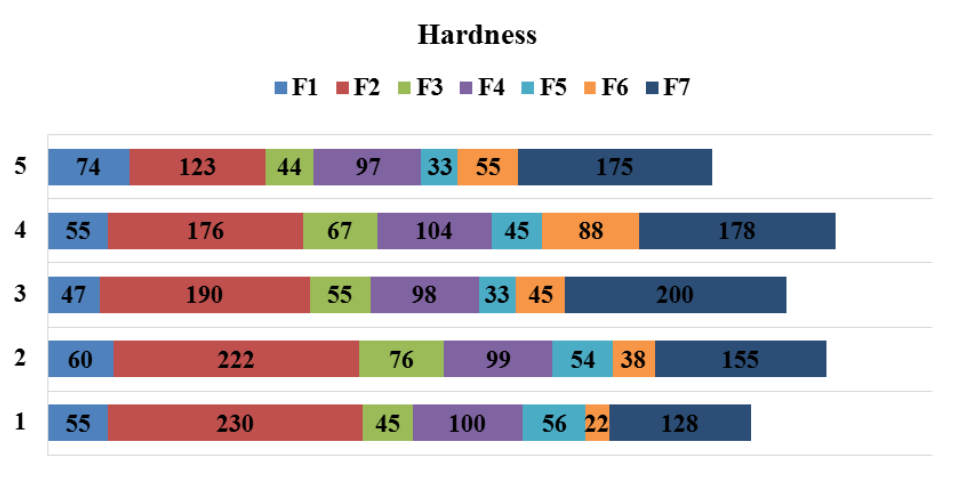


FIG. 7: Hardness of Carvedilol Phosphate Extended Release Tablets.

Table 3: Friabilityof Carvedilol Phosphate Extended Release Tablets.

No. of Tablets	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)
6.5gm (Appri.42 -Tablets)	1.78	0.00	0.19	0.06	0.98	0.92	0.45

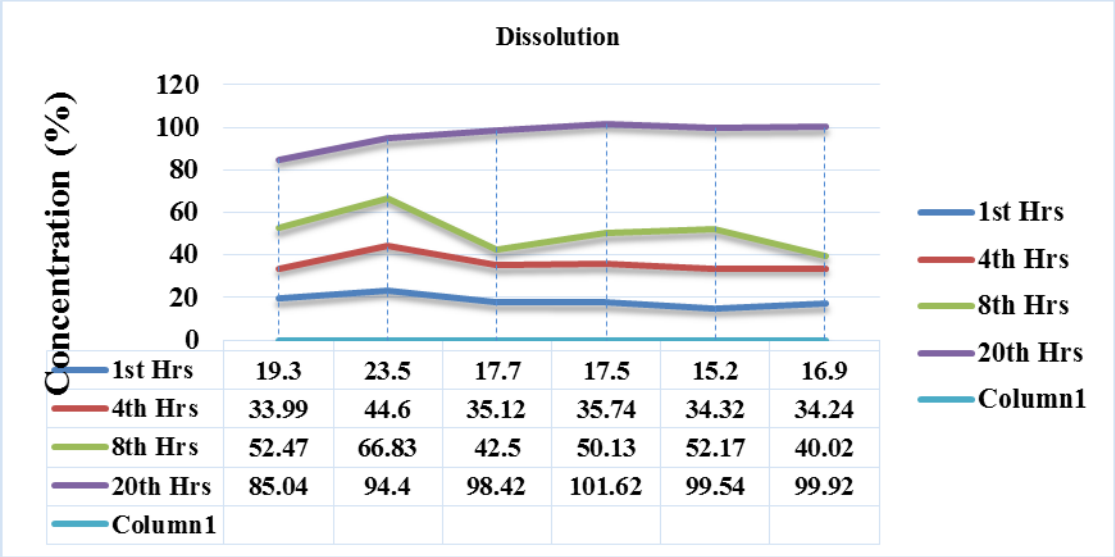


FIG. 8: Dissolution Studies Carvedilol Phosphate Extended Release Tablets.

Table 4: Uniformity of Content By Hplc of Carvedilol Phosphate Extended Release Tablets.

Tablets	Sample Area	Content in mg/tablets	Uniformity content in %	Tablets	Sample Area	Content in mg/tablets	Uniformity content in %
1	4382884	9.94	99.38	6	4411907	10.00	100.04
2	4298772	9.75	97.48	7	4345639	9.85	98.54
3	4399130	9.98	99.75	8	4431104	10.05	100.48
4	4304792	9.76	97.61	9	4414637	10.01	100.10
5	4306333	9.76	97.65	10	4268776	9.68	96.8
Average							98.8
Minimum							96.8
Maximum							100.5
Uniformity content Limit : 85.0% to 115.0%							

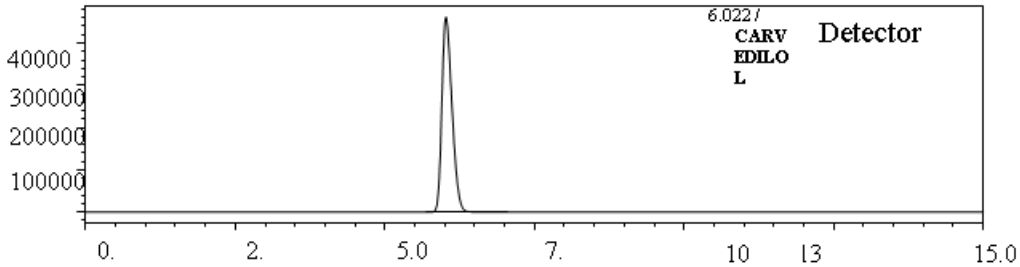


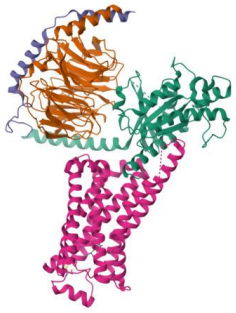
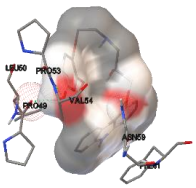
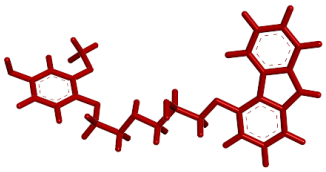
FIG. 9: Assay By Hplc Of Carvedilol Phosphate Extended Release.

Table 5: Assay By Hplc Carvedilol Phosphate Extended Release Tablets.

Ret. Time	Area	Area%	T. Plate	T. Factor	Resolution	R.R.Time	Name
6.022	5462459	100.000	5607	1.339	--	--	CARVEDILOL
	5462459	100.000					

Sample Preparation	Sample weight taken in mg	Sample area	Assay in mg /tablet	Assay in %	Assay Limit:95.0% to 110.0%
1	1550.47	4406879	10.01	100.1	

Table 5: Auto – Docking Analysis Of Carvedilol Phosphate Extended Release Tablets.

Auto - Docking Analysis				
S. No	**3D structure in Biovia viewer**	**Results images**	**Higher Docked Energy/Score**	
	 **MACRO MOLECULES:** PDB CODE: 8ge1	**3letter symbol:** VAL54:HN 0 ASN59:HD21 1 ASN59:HD21 1 	Ligand 1_1 Ligand 2_1 Ligand 3_1 Ligand 4_1 Ligand 5_1 Ligand 6_1 Ligand 7_1 Ligand 8_1 Ligand 9_1 Ligand 10_1	-4.05 -2.52 -2.49 -2.11 -1.61 -1.33 -1.32 -1.2 0.44 -0.02
	SPACING: 0.35 / **RADII: 0.06**			
	LIGAND: 			

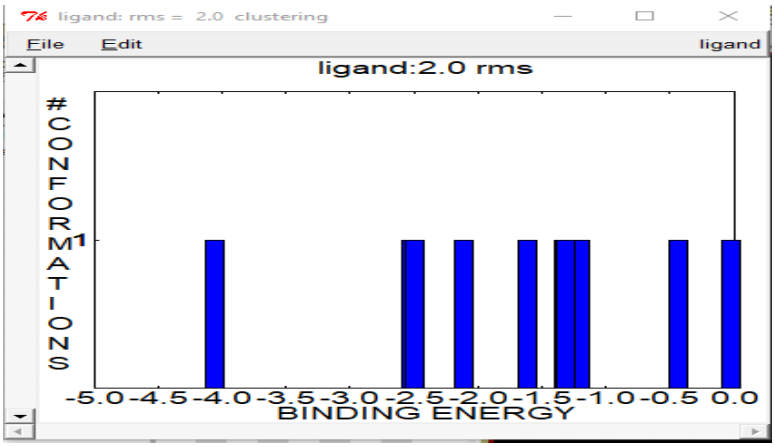


Fig. 10: Binding Energy Of Carvedilol Phosphate Extended Release Tablets.

Table 6: Physiochemical Properties Carvedilol Phosphate Extended Release Tablets.

Formula	C48H60N4O17P2
Molecular Weight (MW)	504.5
No.Heavy atoms	71
No.Aromatic heavy atoms	38
Fraction Csp3	0.25
No.Rotatable bonds	20
No.H-bond acceptors	19
No.H-bond donors	13
MR	267.56
TPSA	335.85

Table 7: Liphophilicity of Carvedilol Phosphate Extended Release Tablets.

iLOGP	4.14
XLOGP3	-1.32
WLOGP	5.55
MLOGP	-1.18
Silicos-IT Log P	4.55
Consensus Log P	2.35

Table 8: Water Solubility of Carvedilol Phosphate Extended Release Tablets.

ESOL Log S	-4.45
ESOL Solubility (mg/ml)	3.63E-02
ESOL Solubility (mol/l)	3.54E-05
ESOL Class	Moderately soluble
Ali Log S	-5.23
Ali Solubility (mg/ml)	5.99E-03
Ali Solubility (mol/l)	5.83E-06
Ali Class	Moderately soluble
Silicos-IT LogSw	-8.14
Silicos-IT Solubility (mg/ml)	7.35E-06
Silicos-IT Solubility (mol/l)	7.16E-09
Silicos-IT class	Poorly soluble

Table 9: Pharmacokinetics Parameters of Carvedilol Phosphate Extended Release Tablets.

GI absorption	Low
BBB permeant	No
Pgp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
log Kp (cm/s)	-13.5
Lipinski No.violations	3

Table 10: Drug-Likeness Properties of Carvedilol Phosphate Extended Release Tablets.

Ghose No.violations	3
Veber No.violations	2
Egan No.violations	1
Muegge No.violations	6
Bioavailability Score	0.17

CONCLUSION

The comprehensive evaluation of post-compression studies for carvedilol extended-release tablets demonstrated that all formulations met the established quality standards, ensuring their suitability for clinical use. The tablets exhibited consistent appearance, uniform weight, and appropriate dimensions, while hardness and friability tests confirmed their mechanical integrity. HPLC analysis verified the identity and uniformity of carvedilol phosphate, and dissolution studies showed effective drug release profiles within specified limits. Additionally, content uniformity assessments indicated reliable dosage accuracy. These findings highlight the successful formulation of carvedilol extended-release tablets, with potential for further optimization to enhance therapeutic performance and patient compliance.

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