Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 11 [7] June 2022 : 193-209

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and Characterization of Osmotically Controlled Bilayer Tablets containing Carvedilol as Antihypertensive Drug

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ABSTRACT

Aim of study was to design, Characterization and Evaluate Self Pore forming Osmotic Tablet containing Antihypertensive Drug. Prior to compression, lubricated blend of Carvedilol tablets was characterized for physical parameters like angle of repose, bulk and tapped densities and % compressibility. Wet granulation method is utilized for the preparation of tablet. The maintenance dose of the drug was given through sustained release layer which was prepared by utilizing polymers like Eudragit RLPO. The coating was carried out in the Pharma R and D coater for 25 tablets with pan speed of 25 rpm, pan temperature of 60-65°, atomizing air pressure of 5-6 psi and spray rate of 1 ml/min. No Drug-drug interaction and Drug-Excipients interactions were found. 3^2 Full-Factorial design was applied to confirm the influence of variables selected. Formulation CD6 for Carvedilol containing were consider for optimized formulation. From the entire study conducted during present investigation can be used to conclude that the developed tablets can be used to treat the hypertension.

Keywords: *Eudragit RSPO/RLPO, Factorial Design, Sustained Release Drug Delivery System, Carvedilol*

Received 17.03.2022 Revised 22.05.2022 Accepted 07.06.2022

INTRODUCTION

One of the important modified drug delivery systems is Osmotic drug delivery system (ODDS) which utilize osmotic pressure as a driving force for controlled delivery of drugs. The release of drug from osmotic system is independent of presence and absence of food, pH of gastrointestinal (GI) tract, GI motility and hydrodynamic conditions of body due to rate controlling semi permeable membrane.[1] When an osmotic system came in contact with water, water diffuses into the core through the micro porous membrane setting up an osmotic gradient and thereby controlling the release of the drug. Osmotic pressure created due to inhibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic devices [2].

Osmotic Drug Delivery as an advanced technique

Osmotic drug delivery operates under the principle of osmosis. The most important goal of osmosis based modified release is to control the delivery rate of an active ingredient, thus increasing the duration of therapeutic action and/or targeting its delivery to a specific organ or tissue. [3] These advances accomplished to the development of osmotic pumps, which are a form of a membrane-controlled release drug delivery system by using osmotic pressure as a driving force [4].

Self-pore forming osmotic drug delivery systems:

Figure 1 corresponds to the controlled porosity osmotic drug delivery (CPDD). These systems are alternatively known as Osmotically Controlled Self-Pore drug delivery system. Tablet dosage form imbibed with this technology gaining the significant attention of formulation scientists. In this technology osmotic tablet may be formed wherein the delivery orifices (holes) are formed in situ through leaching of water-soluble pore-forming agents incorporated in semipermeable membrane (SPM) (e.g., urea, nicotinamide, sorbitol, etc.). Drug release rate from Osmotically Controlled Self-Pore drug delivery system is dependent on a variety of factors like coat thickness, drug solubility, proportion of leachable pore-forming agent(s) and the osmotic pressure gradient across the membrane [5,6].

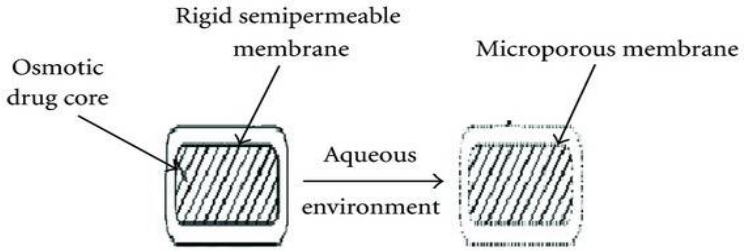

Figure 1: Self pore forming controlled osmotic drug delivery

Carvedilol phosphate is a beta blocker widely used for the treatment of hypertension. Its short biological half-life and thus frequent administration (usually three to four times a day) makes it a suitable candidate for controlled release and/or sustained release (CR/SR) preparations. Carvedilol phosphate is a low soluble drug and the release rate of carvedilol phosphate from oral osmotic pumps is usually low. Due to low solubility of carvedilol phosphate, it is difficult to formulate osmotic tablet. In present study, solubility of carvedilol phosphate was increased with addition of polysorbate 80 in the system. Polysorbate 80 increases its solubility and dissolution. Prepared osmotic tablet of carvedilol phosphate gives drug release for up to 24 hr. by osmotic mechanism.[7,8,]

Candidate drugs for osm81otic drug delivery have water solubilities of 50-300 mg/ml. High soluble drugs would show a high release rate that would be zero order release for very small percentage of initial drug load. Thus, intrinsic water solubility of many drugs might preclude them from incorporation into osmotic drug delivery system. By modulating the solubility of drug within core, effective drug release can be obtained for even poor candidate drugs for osmotic drug delivery. This approach can be used for conversion of first order profile into zero order profile without altering the chemical structure.

Controlled porosity osmotic tablet contains core tablet coated with semipermeable membrane which allows active agent to come outside through pores formed in situ. The controlled-porosity osmotic pump has been developed via incorporation of leachable water-soluble small molecules, such as sodium chloride, potassium chloride, urea, and sucrose etc. into major component of film coating material2–4. These pore-forming agents are leached when contacted with an aqueous medium, and the pores are created on the surface to allow drug release. Plasticizer can also be used as pore forming agent. Plasticizer has been used to modify not only the mechanical properties but also the thermal property, water absorption behavior, and adhesive property of polymeric films. All of these properties affect the strength of coating films and the integrity of final products, which further affect drug release performance. Many compounds can be acted as a function of plasticizer including poly (ethylene glycol), propylene glycol, sorbitol, urea, oil, citrate, adipate, and phthalate, etc. The release of drug is dominated by thickness of coating films, the level of water-soluble components, the solubility of drug, and the osmotic pressure difference. The advantage of blending of pore-forming agent avoids using high technical laser beam to drill an orifice for drug release, in additional, it is easily fabricated via traditional film coating technique [9,10]. To study, the formulation and Evaluation of Controlled Release Osmotic Tablet of Carvedilol Phosphate"

Rationale

- Carvedilol Phosphate is a nonselective β-adrenergic blocking agent with α1-blocking activity.
- It is safe and effective in the treatment of hypertension, left ventricular dysfunction and heart failure.
- Carvedilol Phosphate is quickly and extensively absorbed via oral administration with an absolute bioavailability 25% - 35% due to a significant degree of first-pass metabolism.
- Carvedilol Phosphate has a short half-life of 7 hours.
- Long-term therapy in hypertension by Carvedilol Phosphate may result in poor patient compliance since it has low bioavailability and short half-life, leading to increased frequency of administration.
- Controlled release Carvedilol Phosphate formulation is therefore necessary for improving patient compliance and reducing frequency of administration.
- The release of Carvedilol Phosphate can be extended and controlled by making it in Osmotic tablet, which are a class of novel drug delivery systems because of their so many advantages such as less frequent administration to produce the desired constant plasma concentration associated with improved patient compliance and controlled drug delivery.
- Hence, the present study was intended towards the development of controlled release formulations of Carvedilol Phosphate based on osmotic technology. In this study, osmotic drug delivery systems for Carvedilol Phosphate were developed.

MATERIAL AND METHODS

Table 1 Materials Used in the Preparation of carvedilol tablet

Sr.No.	Material	Function	Sources of Material
1.	Carvedilol Phosphate	API	Rivera Pharma, Surat, Gujarat
2.	Microcrystalline Cellulose,	Diluent	Loba Chem
3.	Mannitol, Sodium Chloride	Osmotic agent	Loba Chemie, Ambala Cantt
4	Cellulose Acetate	Coating polymer	Loba Chemie, Ambala Cantt
5	Low-substituted HPC	Binder	Loba Chemie, Ambala Cantt
6	PEG 400	Plasticizer	Loba Chemie, Ambala Cantt
7	Povidone K30	Pore-Former	Loba Chemie, Ambala Cantt
8	Magnesium stearate	Lubricant	Loba Chemie, Ambala Cantt
9	Talc	Glidant	Loba Chemie, Ambala Cantt

Table 2 Table List of Equipment's

S. N.	Equipment's	Manufacturers
1.	Digital weighing balance	Reptech weighing balance ltd., Ahmadabad
2.	Tablet compression machine	Multipitch Tablet compression machine, Cadmach machinery Co. Pvt. Ltd, Ahmedabad.
3.	Dissolution apparatus	Electro lab ltd, Mumbai
4.	U.V. Visible Spectrophotometer	Shimadzu-1601, Kroyoto, Japan.
5.	pH meter	Systronic, 361-micro pH meter.
6.	Roche Friabilator	Camp-bell Electronics, Mumbai, India
7.	Hardness Tester	Validated dial type, Model:1101, Shivani Scientific Industries Pvt. Ltd.,
8.	Infrared spectrophotometer	Bruker, USA
9.	Differential scanning calorimeter	DSC TA-60, M/s Shimadzu
10.	Tablet Coating Machine	Solace Ltd.

EXPERIMENTAL

Preformulation Study [5,6,7,8,9]

Organoleptic properties

Drug is characterized for its colour, odor and taste results were reported utilizing descriptive terminology.

Melting Point Determination:[5,6]:

Melting point of Carvedilol was determined by taking a small amount of drug in a capillary tube closed at one end and was placed in melting point apparatus and temperature range at which the drug melts was noted and compared with reference value.

Solubility studies:[7, 8]

Solubility plays an important part in the Preformulation study as it gives an idea about the BCS class of the drug and plays a pivotal role in the selection of dissolution media, which in turn helps in designing the formulation. Solubility study was performed in Water and buffers with relevant physiological pH (1.2, 4.5, 6.8) at 37°C.

Analytical Method for Estimation of the Drug:

In Preformulation studies it is very important to establish a simple UV-Visible Spectrophotometric analytical method to quantify the drug accurately in various tests.

UV Absorption:[9]

Carvedilol Phosphate dissolved in selected solvents and further diluted suitably. These solutions were scanned in the range 200 to 400 nm against respective blank to determine wavelength of absorption maxima or λmax.

Standard Calibration Curve: [10,11]

Drug (100 mg) was taken and to this 40 ml of methanol was added and shaken for about 20 min on mechanical shaker to obtain a clear solution. To this 0.1N HCl was added to make up the volume up to 100 ml. From above solution various dilutions were prepared to get concentrations of 5, 10, 15, 20 and 30 mcg/ml. The absorbance of the various solutions was measured against methanolic HCL as a blank at 238 nm using double beam UV visible spectrophotometer. The graph of absorbance v/s concentration was plotted and data were subjected to linear regression analysis in Microsoft excel.

Drug-excipient compatibility studies for Carvedilol

Drug-excipient compatibility studies is a quick scientific approach for accepting/rejecting excipients for use in pharmaceutical formulations. These are used to rapidly assess stability / incompatibility between drug and proposed excipients.

Drug - Excipients Compatibility Study of carvedilol by DSC [12,13].

The physical mixtures of drug with different excipients for compatibility studies were prepared by triturating drug and excipients in a dried mortar for 5 min. and Differential scanning Calorimetry (DSC) was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter. The instrument comprised of calorimeter (DSC 60), flow controller (FCL 60), thermal analyser (TA 60) and operating software (TA 60). The samples (drug alone or mixture of drug and excipients) were heated in sealed aluminium pans at a scanning rate of 5 ^{0}C/min from 50 to 350^{0}C. Empty aluminium pan was used as a reference. The heat flow as a function of temperature was measured for the drug and drug-excipient mixture.

Drug - Excipients Compatibility Study of carvedilol FT-IR [12, 13]

The infrared spectra were obtained using an FT-IR spectrophotometer. A pellet of Carvedilol, with other excipients and dry potassium bromide was prepared using hydraulic pellet press at a pressure of 7 to 10 tones. FT-IR spectra of drug and excipients were taken in the range of 400- 4000 cm-1 by using Perking Elmer spectrum GX FT-IR. A FT-IR spectra was compared with FT-IR spectra of pure drug.

Screening of polymer for preparation of carvedilol self-pore forming tablet:

Preliminary Trial Batches for Selection of Polymers without and with agent:

Table 3: Composition of Preliminary Trial Batches for Selection of Polymers

	Optimization of Sorbitol			Optimization of Sodium chloride: potassium chloride			Optimization of Povidone K 30			Optimization Of coating wt. gain
Ingredient	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**
Core	**Mg/tab**										
Carvedilol Phos.	54.24	54.24	54.24	54.24	54.24	54.24	54.24	54.24	54.24	54.24	54.24
Micro-Cellulose	64.76	39.76	14.76	29.76	19.76	9.76	32.26	31.01	28.51	20.45	12.38
Pregela. Starch	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
Low-subst. HPC	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Nacl: KCl	-	-	-	**10.00**	**20.00**	**30.00**	10.00	10.00	10.00	10.00	10.00
Sorbitol	**50.00**	**75.00**	**100.0**	**75.00**	**75.00**	**75.00**	75.00	75.00	75.00	75.00	75.00
Talc	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Mag. Stearate	10.0	10.0	10.	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Coat	**Mg/tab**										
Eudragit RLPO and RSPO	25.0	25.0	25.0	25.00	25.00	25.00	25.00	25.00	25.00	31.25	37.50
PEG400	3.50	3.50	3.50	3.50	3.50	**3.50**	**3.50**	**3.50**	**3.50**	**4.38**	**5.25**
Dical. Phosphate	q. s	q. s	q. s	q. s	q. s	**q.s**	**q. s**	**q. s**	**q. s**	**q. s**	**q. s**
Amaranth 3%	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Total	250.00	250.00	250.00	25	250.00	250.00	25	250.00	250.00	25	250.00

				0.000			0.000			0.000	

METHOD OF PREPARATION OF CARVEDILOLCORE TABLETS:

Wet granulation method was used to prepare granules. PVP K30 was used as a binder and osmogene was used of combination of NACL and KCL in equal proportion. For the preparation of tablet, dried granules were allowed to pass through standard mesh no.16# and softly mixed with talc and magnesium stearate. The uniform blended mixture was then compressed into tablets (250 mg each) using 8mm diameter, deep concave punches in a 12-station compression machine. Compression force was attuned to provide tablets with hardness of approx. 5 kg/cm2 on a Monsanto tablet hardness tester.

Coating of core tablet

For coating solution, required amount of eudragit RLPO and RSPO were dissolved in sufficient amount of isopropyl alcohol: acetone (30:70) at 40° in a thermostat water bath. To this solution, appropriate number of plasticizers like peg400 and butylphthalide were added. Aqueous pore forming agent (70% w/w sorbitol) was dispersed in methanol and added to solution of eudragit polymers with sunset yellow as coloring agent. A fine dispersion was formed, which was then shaken manually for 10-15 min to uniformly disperse the pore forming agent and coloring agent. The coating was carried out in the pharma r and d coater (ideal cures pvt Ltd) for 25 tablets with pan speed of 25 rpm, pan temperature of 60-65°, atomizing air pressure of 5-6 psi and spray rate of 1 ml/min. The tablets were coated till 5% weight gain was obtained. Coated tablets were further air dried for 24 h.

Coating Process:

Core tablets obtained as per above explained process were coated using a Tablet coater using previously described solution. The tablets were then evaluated for post compression parameters of Osmotic Controlled Release Tablet.

Table 4: Composition of Coating Solutions

Ingredients	**C1**	**C2**	**C3**	**C4**
Eudragit RLPO and RSPO	25	**30**	25	30
PEG400	10	**10**	10	10
Sorbitol (% w/v)	0.5	**0.5**	1	1
Acetone (ml)	100	**100**	100	100
Amaranth 3%	Q. S	**Q. S**	Q. S	Q. S

FORMULATION DEVELOPMENT

Optimization of Formulation Variables using 3^2 full factorial design:[16].

On the basis of literature survey on control porosity osmotic pump carvedilol tablet and result of preliminary trial batches it was concluded that mainly two formulation variables effect on physicochemical parameters of tablet.

The trial-and-error method was time consuming and it may be taking more efforts to develop an ideal formulation using this traditional technique since the joints effect of independent variable are not considered. It was therefore essential to understand the complexity of pharmaceutical formulation using build statistical tools like factorial design in addition to art of formulation; this technique was effective method of indicating the relative significance of a number of variable and their interaction.

A statistical model embodied interactive and multinomial terms was used to evaluate the response. The number of experiments required for the studies is independent on the number of independent variables selected the response is measure for each trial.

$$\mathbf{Y=\beta_0+\beta_1X_1+\beta_2X_2+\beta_{12}X_1X_2+\beta_{11}X_1^2+\beta_{22}X_2^2+\varepsilon}$$

Where, Y is the dependent variable,β_0 is the arithmetic mean response of the nine run and

$\beta_i$is estimated coefficient for X_i

The main effect (X1and X2) shows the average result of changing lower to high value of one factor at a time. The interaction (X_1X_2) showed how the response changes when two factors are modified at similar time. In the present study a 3^2 full factorial design was utilized. In this design two factors were evaluated, each at three level, and experimental trial were performed at all nine workable combinations. The concentration of sodium chloride: potassium chloride (X1) and amount of sorbitol (60%w/w) (X_2) were selected as independent variables. The Dependent variables, first, time for 50% drug release ($t_{50\%}$) and second, time for 90% drug release ($t_{90\%}$) were selected as dependent variable.

Table 5: Independent and Dependent Variable of Formulation

	Level	**X_1 Amount of polymer mixture**	**X2 Amount of pore former**

Independent Variable		(NaCl: KCl)	(mg)
	Low	25	15
	Medium	30	20
	High	40	30
Dependent Variable	% Drug release (t50%)		
	% Drug release (t 90%)		

Formulation Optimization of Carvedilol self-pore forming Tablet using 3^2 Full Factorial Design

Table 6: 3^2 Full Factorial Design of Batches C1-C9

3^2 Full Factorial Design Layout				
Batch No.	Independent Variable			
	Coded value	Amount of polymer mixture (NaCl: KCl) (mg)	Coded value	Amount of pore former (mg)
CD1	-1	25	-1	15
CD2	-1	25	0	20
CD3	-1	25	1	30
CD4	0	30	-1	15
CD5	0	30	0	20
CD6	0	30	1	30
CD7	1	40	-1	15
CD8	1	40	0	20
CD9	1	40	1	30

Statistical Analysis:

For optimization 3^2 full factorial design was employed to study the effect of independent variable on dependent variable % drug release($\%t_{50}$) and % drug release (t90%). All the batches were prepared according to the design and analysed using the design expert 13 software. The software suggested quadratic model and gave model equation for all dependent variables. The results of ANOVA along with response surface and contour plots generated for each response are given in table and figure respectively. Validation of optimization design and overlay plot for combined effect of concentration of polymer ratio and amount of effervescent agent are shown in figure.

Characterization of carvedilol self-pore forming Tablet:

Carvedilol osmotic pore forming tablet was characterized by determined the precompression parameters as well as post- compression parameters. In post compression parameters hardness, weight variation, friability, in vitro drug release study was evaluated.

Pre-compression Parameters of Powder Blend of carvedilol self-pore forming Tablet:

Bulk Density: [17,18] Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another.

$$BulkDensity = \frac{WeightofthePowder}{VolumeofPowder}$$

Tapped density:**[17,18]**

Tapped density is the ratio of the mass of the material to the tapped volume of material. tablet blend was poured into graduated cylinder. then, the cylinder was allowed to 100 taps under its own weight onto a hard surface. tapped density was calculated using following equation.

TAPPED DENSITY=M/V

Where M is weight of powder(G),V is tapped volume (Ml)

Compressibility Index:[17,18]

The compressibility index was calculated from the bulk and tapped density value by following equation;

$$Carr'sIndex = \frac{TappedDensity - BulkDensity}{TappedDensity} X\ 100$$

Table 7:Grading of the Powders According to Carr's Index

Compressibility Index (%)	Flow Character
10≤	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very poor

Hausner's Ratio:[18]
The Hausner's ratio was calculated from the following equation:

$$HausnerRatio = \frac{TappedDensity}{BulkDensity}$$

Table 8: Grading of the Powders According to Hausner's Ratio

Hausner's Ratio	Flow Character
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.34-1.45	Poor
1.46-1.59	Very poor
>1.60	Very, very poor

Angle of repose:[18]
The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, there by evaluating the flow ability of the granules. Height of the pile was also measured.
$\theta = \tan^{-1}(h/r)$ Where, θ is the angle of repose, h is the height, r is the radius.

Table 9: Relationship between angle of repose (θ) and flow properties

Angle of repose	Flow character
<25	Excellent
25-30	Good
30-40	Passable
>40	Poor

Post Compression parameters of carvedilol self-pore forming Tablet:
Hardness: [19,20]
To avoid damage due to mechanical shocks of handling in manufacture, packaging and shipping tablets required physical strength or hardness. Tablet hardness tester was used to measure tablet hardness. Its unit is kg/cm^2. The experiment was performed in triplicates for all formulation batches and from that an average and standard deviation values were calculated.
Thickness: [19,20]
Tablet thickness can be measured using a simple procedure. Three tablets were taken and their thickness was measured using vernier callipers. The thickness was measured by placing tablet between two arms of the vernier callipers. Its unit is mm.
% Friability Test
It was performed to check damage occur during mechanical shock or attrition. Roche Friabilator was mainly used for to detect tablet friability. Its unit is percentage (%). Ten tablets were initially weighed (W0) and transferred into Friabilator. The Friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by –
%F = 100 (1-W0/W) % Friability of tablets less than 1% are considered acceptable.
Weight Variation Test
To determine tablet weight uniformity, 30 tablet were sampled and accurately weighed using an electronic analytical balance. The results were expressed as mean values of 30 determinations. The coefficient of variation was calculated using the Formula: Coefficient of variation (%) = Standard deviation / Mean × 100

Table 10: Weight Variation limit according to USP

Average weight of tablet (mg)	Maximum % difference allowed
130 or less	10
130 to 324	7.5
More than 324	5.0

Drug Content:20 tablets were weighed and powdered. Blend equivalent to 100mg of Carvedilol Phosphate was weighed and transferred to 100 ml volumetric flask. To it 50 ml of 0.1N HCl was added and shaken until drug was completely dissolved. The solution was made up to 100 ml with 0.1N HCl and suitably diluted to similar concentration as that of the standard to obtain sample solution. [22,23]

***In vitro* drug release: [24,25,26]** USP type II (paddle type) dissolution apparatus (TDT-08l, Electrolab, Mumbai, India) were used for dissolution studies in 900 ml medium at 37 ± 0.5° at a rotation speed of 50 rpm. All nine batches of tablets were transferred to the dissolution medium containing 900 ml of 0.1 N HCl for first 2 h followed by phosphate buffer pH 6.8 for remaining 22 h. The dual pH dissolution medium was used to simulate physiological conditions as specified in Indian Pharmacopoeia (IP) 2014[21], for sustained release preparations. At 1 h interval, aliquots of 1 ml were withdrawn, filtered and absorbance was measured by UV spectrophotometer at 238nm. The medium was replaced with equal volume of fresh dissolution medium to maintain sink conditions.

Stability study: [27,28] Carvedilol Phosphate CPOP (optimized batch) were kept for one month and the stability of the tablets monitored up to 1 month at accelerated stability conditions (40 ºC temperature and 75±5% RH). Samples will be removed and characterized by Appearance, Hardness, Friability, Disintegration Time, in-vitro drug release study and drug content.

RESULT AND DISCUSSION

Drug identification and characterization

Melting point determination:

The melting point of the Active Ingredient was found to be 114°C, which is found to be consistent with that of reported melting point of pure Carvedilol Phosphate. This confirms the purity of the material.

Solubility Studies:

Solubility of pure Carvedilol Phosphate was evaluated in different media and the results were recorded in the table below. Results are tabulated below:

Table 11: Solubility Studies Data

Sr. No.	Media	Solubility (mg/ml)
1	Purified Water	0.059 ± 0.03
2	Ph 1.2 HCl buffer	2.512 ± 0.04
3	Ph 4.5 acetate buffer	0.547 ± 0.06
4	Ph 6.8 phosphate buffer	0.0612 ± 0.03

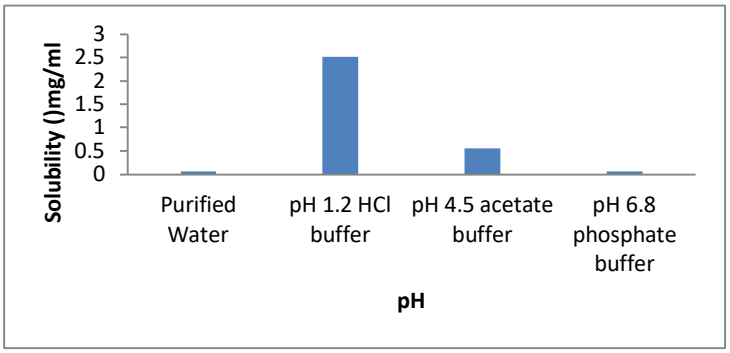

Figure 1: solubility of drug at different pH

ANALYTICAL METHOD DEVELOPMENT BY UV SPECTROSCOPY

UV Absorption

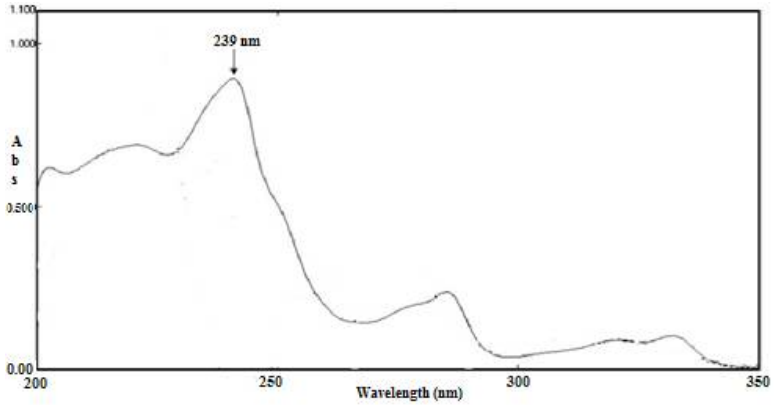

Figure 2: λmax of Pure Carvedilol Phosphate

Scanning the Carvedilol Phosphate stock solution showed that the λmax of drug was 239nm and all further analysis will be done at this particular wavelength.

STANDARD CALIBRATION CURVE

TABLE 12: Standard calibration curve of carvedilol phosphate in 0.1N HCL

Sr. No.	Concentration (µg/ml)	Avg. Abs ± SD
1.	5	0.158 ± 0.013
2.	10	0.326 ± 0.027
3.	15	0.500 ± 0.047
4.	20	0.638 ± 0.032
5.	25	0.817 ± 0.067
6.	30	0.990 ± 0.093

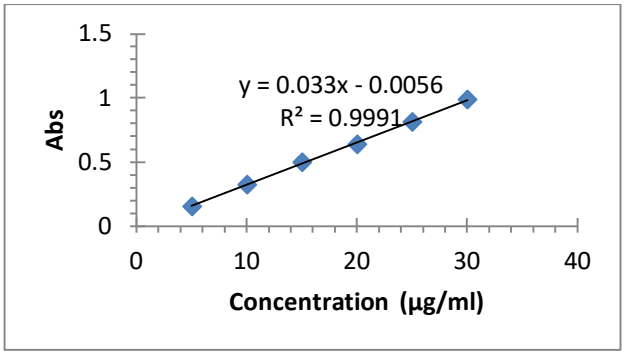

Figure 3: Standard calibration curve of Carvedilol Phosphate in 0.1NHCl

Table 13: Standard calibration curve of Carvedilol Phosphate in 6.8 phosphate buffer

Sr. No.	Concentration (µg/ml)	Avg. Abs ± SD
1.	5	0.162 ± 0.010
2.	10	0.328 ± 0.024
3.	15	0.502 ± 0.043
4.	20	0.653 ± 0.031
5.	25	0.824 ± 0.064
6.	30	0.994 ± 0.091

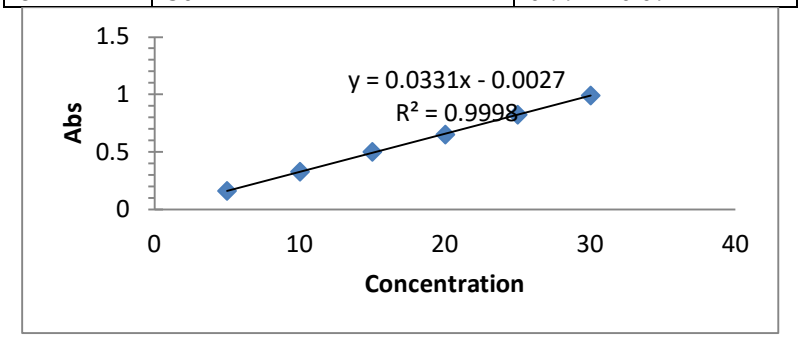

Figure 4: Calibration Curve in 6.8 phosphate buffer

DISCUSSION

Regression coefficient for the drug in simulated vaginal fluid was found to be near to one and in the linearity range. This standard calibration curve method follows lambert's beers law and found to be suitable for the determination of drug content and in-vitro release study.

Drug excipient Compatibility study

The identification of the pure drug was done by differential scanning calorimetry. Pure carvedilol phosphate shows melting range of between 114°c-123°c. DSC trace wherein the melting endotherm was found at 117.6°c.

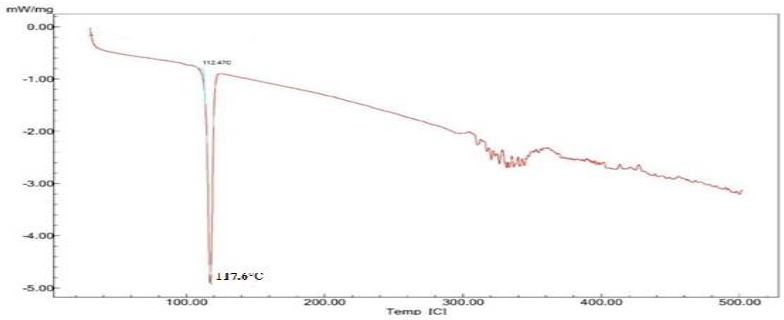

FIGURE 5 DSC curve of pure carvedilol phosphate

FT-IR STUDIES

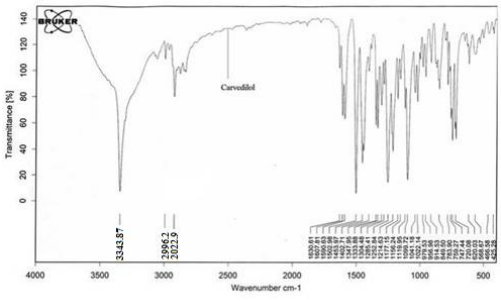

Figure 2.6: FT-IR spectra of Pure Drug

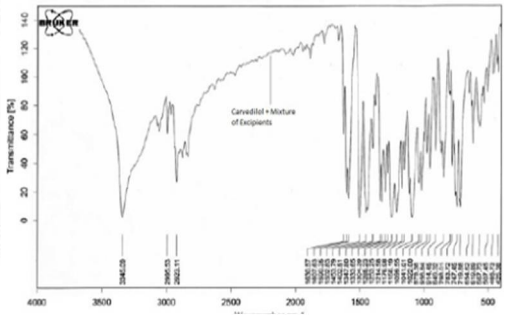

Figure 2.7:FT-IR of Carvedilol Phosphate Phosphate+ Excipients

The figure above shows that there is no change in the FTIR pattern of all the functional groups of Carvedilol Phosphate is present in the physical mixture of drug and excipients. Characteristic peaks like –OH (3600-3200cm^{-1}), –CH_3(1465-1440cm^{-1}) and –NH (3500-3300 cm^{-1}) are consistent in both FT-IR graphs. Hence, it can be concluded that the excipients selected are compatible with the drug and can be used for further evaluation.

Evaluation Parameters for Preliminary Screening of Polymers With osmotic and pore forming agent

Pre-Compression Parameters:

TABLE 14: Results of pre-compression parameters of blend

Formulations	Angle of Repose(θ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Consolidation Index (%)	Hausner's Ratio
C1	28.4±1.9	0.3142±0.03	0.4357±0.09	10.886±0.90	1.127±0.06
C2	31.6±1.2	0.3256±0.04	0.4419±0.18	11.318±1.20	1.157±0.05
C3	33.1±0.9	0.3371±0.03	0.4520±0.08	16.420±1.29	1.141±0.09
C4	29.3±1.3	0.3487±0.05	0.4680±0.07	12.491±1.21	1.242±0.08
C5	27.0±0.8	0.3612±0.06	0.4797±0.16	14.703±1.22	1.328±0.12
C6	25.3±0.7	0.3656±0.05	0.4873±0.18	13.974±0.95	1.333±0.13
C7	28.7±1.5	0.3423±0.08	0.4671±0.12	16.718±0.93	1.265±0.10
C8	29.1±1.3	0.3439±0.09	0.471±00.22	14.985±0.81	1.170±0.13
C9	28.6±1.5	0.3477±0.08	0.4672±0.08	15.578±1.16	1.244±0.08
C10	28.9±0.8	0.3500±0.07	0.4728±0.09	15.973±1.19	1.351±0.08
C11	27.2±0.7	0.3488±0.06	0.4690±0.07	16.629±0.85	1.245±0.05

(Where n=3, Mean ± SD)

Discussion: The pre-compression parameters of all preliminary trial batches shown that blend had good flow property according Hausner's ratio and Carr's index ranges. From the above result of pre compression parameters, formulation batches C1, C2, C4,C6, C8, C9, C10 had angle of repose between 26.39±0.97º to29.92±0.84º which showed good flowability, formulation batches C1, C2, C3, C4, C8, and C10 had Carr's index between 10.90±0.063 to 15.78±0.047 which showed good compressibility of powder blend, and formulation batches C1, C2, C3, C4, C5, C8, C10 had showed less than 1.19 Hausner's ratio which indicates good flowability of powder blend.

POST COMPRESSION PARAMETERS:

TABLE 15: Results of Post-Compression Parameters

	Weight	Thickness	Hardness	Friability	

Formulation	Variation (%)	(mm)	(kg/cm²)	(%)	Assay (%)
C1	104.4±3.7	1.4±0.12	6.3±0.35	0.216±0.031	100.2±0.2
C2	102.8±3.9	1.2±0.13	4.7±0.45	0.110±0.021	99.9±0.5
C3	101.9±2.4	1.4±0.42	4.2±0.21	0.184±0.054	99.8±0.6
C4	98.3±3.7	1.3±0.21	7.5±0.32	0.241±0.074	98.9±0.7
C5	99.9±4.1	1.4±0.32	5.5±010	0.173±0.056	98.6±0.1
C6	251.4±3.1	1.2±0.50	4.4±0.96	0.213±0.031	101.2±0.3
C7	250.9±2.9	1.3±0.63	7.5±0.21	0.160±0.054	99.7±0.5
C8	252.1±2.6	1.3±0.09	7.8±0.41	0.289±0.032	99.9±0.8
C9	251.6±2.4	1.3±0.11	7.4±0.33	0.227±0.009	100.1±0.9
C10	250.3±2.3	1.4±0.52	7.7±0.09	0.189±0.004	100.2±0.8
C11	251.3±2.5	1.3±0.31	7.2±0.14	0.167±0.011	99.3±1.0

(Where n=3, Mean ± SD)

Weight Variation of all the Formulations was found well within the prescribed Pharmacopoeia limits of NMT 5.0%. A good flow could be attributed to diluent selection and granulation process which has substantial effect on powder flow. All the formulations were compacted to achieve a target hardness of 15 kg/cm². All formulations showed little to no variation in thickness because of high polymer concentration in the formulation. Target Hardness was optimized to 15 kg/cm² keeping in mind the tablet weight and dimensions. All formulations were easily compressible as it had sufficient binder and polymer quantity to be compacted. A high hardness was selected as the coating process would last long and a lower hardness could lead to chipping and core erosion during coating process. Friability for all the formulation was well below the Pharmacopoeia limit of NMT 1.0%. Proper selection of hardness and a good compatibility of the blend resulted in a satisfactory friability result. Friability is an important Quality Attribute as a poor friability may lead to complications during coating process. The main aim of the study was to develop a formulation which would sustain the drug release for a period of 24 hours.

Effect of Osmogene: From the release pattern it was found that Sodium Chloride is a much more potent osmogene when compared to Mannitol, which was supported by literature, claiming that Osmotic capacity of NaCl was 356 and of Sorbitol was 38. So, a mixture of both was optimized to obtain a zero-order release. Since varying quantities of osmogenes changes release rate of the drug, it can be concluded that osmosis is the driving force for drug release from the tablets.

Effect of Preforming agent: Povidone K30 was selected as pore-former for coating. As Povidone is soluble in water, it solubilises itself on contact with water and forms channels through which solute can come out. It is evident from the dissolution results that increasing pore former concentration in the coating increases drug release rate from the tablet.

Effect of % weight gain of coating agent: The choice of polymer for osmotic tablet was Cellulose Acetate, which forms a semi-permeable membrane, i.e., it allows entry of water in the tablet but does not allow the solute to pass through it. So, increasing the concentration of the polymer will increase the barrier for the solute to pass through the membrane, hence, retarding the rate of dissolution. Based on all physicochemical attributes, formulation C4 was found to be the best optimized batch and can be studied further.

***In-vitro* Drug Release Study of Preliminary Trial Batches**

Table 16: Results of Dissolution Studies

	1 hour	2 hours	3 hours	4 hours	6 Hours	8 hours	12 hours	16 hours	20 hours	24 hours
C1	1.5	3.9	6.2	9.2	13.4	19.4	27.3	37.4	48.2	58.8
C2	2.3	4.5	8.4	12.4	16.3	22.4	32.1	44.3	53.6	65.3
C3	3.1	5.2	9.3	14.0	20.1	27.4	39.4	52.1	65.3	78.4
C4	5.4	9.7	14.9	19.4	27.3	35.4	51.6	66.7	84.2	100.3
C5	13.0	23.9	33.1	42.7	55.4	66.6	84.1	98.3	99.7	99.9
C6	21.4	39.7	52.7	65.4	81.6	92.7	99.4	99.5	99.4	99.6
C7	0.5	2.7	4.3	8.1	12.4	19.6	25.3	33.8	38	44.2
C8	2.9	4.8	9.7	15.3	22.1	28.6	39.7	51.3	63.7	74.8
C9	6.7	12.6	18.6	24.6	37.4	51.4	75.9	99.6	100.1	99.9
C10	4.6	7.4	11.3	18.4	23.1	34.7	48.7	64.3	80.9	94.6
C11	3.9	6.6	10.7	17.3	21.7	33.4	45.1	60.7	76.5	89.8

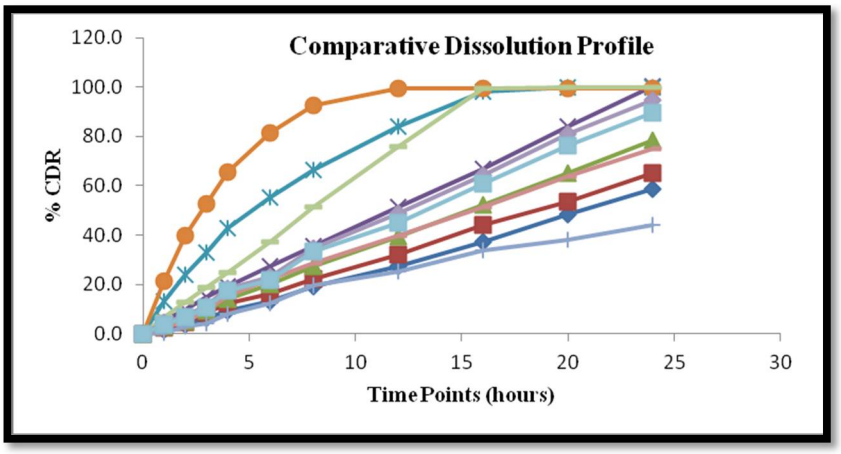

Figure 8: Comparative Dissolution Profile of Formulation Optimization

EVALUATION PARAMETERS OF FORMULATION OPTIMIZATION OF CARVEDILOL SELF-PORE FORMING TABLET USING 3^2 FULL FACTORIAL DESIGN

TABLE 17: PRE-COMPRESSION PARAMETERS:

Formulation code	Angle of repose(θ°) Mean± S. D	Bulk density gm/cm3) Mean± S. D	Tapped density (gm/cm3) `Mean± S. D	Compressibility index (%) Mean± S. D	Hausner's ratio Mean± S. D
CD1	30.48± 1.17	0.62±0.05	0.76±0.03	18.42±0.40	1.22±0.02
CD2	30.79 ± 0.94	0.61±0.02	0.77±0.04	20.77±0.57	1.26±0.05
CD3	29.45± 0.59	**0.62±0.02**	**0.73±0.01**	15.58±0.17	1.17±0.03
CD4	28.04 ± 0.73	0.65±0.01	0.77±0.02	21.51±0.34	1.18±0.07
CD5	27.1 ± 0.7	0.62±0.04	0.79±0.06	14.86±0.46	1.27±0.01
CD6	**25.3 ± 0.8**	**0.63±0.02**	**0.74±0.04**	**15.06 ± 0.14**	**1.17±0.01**
CD7	28.9 ± 1.6	0.68±0.04	0.79±0.01	15.58±0.17	1.16±0.03
CD8	29 ± 1.3	0.64±0.03	0.77±0.03	21.51±0.34	1.20±0.008
CD9	28.8 ± 1.6	0.66±0.03	0.75±0.04	14.86±0.46	1.73±0.01

(Where n=3, Mean ± SD)

The granules prepared for nine batches of tablet formulations were evaluated for flow and compression properties. All batches of granules showed excellent flow properties with angle of repose value between 25-33°. The packaging capacity of granules was evaluated by measuring bulk and tapped density and found respectively between 0.31- 0.38 gm/ cm^3 and 0.43-0.48 gm/ cm^3. Compressibility of granules was determined using bulk and tapped density. The car's index was found in the range of 24-28% suggesting excellent compression ability of granules. The Hausner's ratio values were found in the range of 1.32-1.38, indicating excellent flow and compression properties of granules.

Post compression parameters:

Table 18: Post-compression Data CD1 to CD9 Batches of Full Factorial Design

Formulation Code	Average Weight (mg) Mean ± S. D	Hardness (kg/cm^2) Mean± S. D	Thickness (mm)	Friability (%)	Drug content (%) Mean± S. D
CD1	104.9 ± 3.7	15.1 ± 4.6	2.9±0.05	0.61±0.04	98.2 ±0.2
CD2	101.8 ± 3.9	15.0 ± 5.1	2.7±0.06	0.67±0.03	99.9 ± 0.5
CD3	99.9 ± 2.4	14.9 ± 7.3	2.9±0.03	0.37±0.03	99.8 ± 0.6
CD4	102.3 ± 3.7	15.1 ± 6.4	2.8±0.03	0.56±0.10	98.9 ± 0.7
CD5	103.9 ± 4.1	15.0 ± 7.4	2.9±0.03	0.37±0.14	98.6 ± 0.1
CD6	**100.4 ± 3.1**	**14.8 ± 6.1**	**2.9±0.02**	**0.72±0.06**	**101.2 ±0.3**
CD7	101.9 ± 2.9	14.9 ± 5.5	2.8±0.02	0.61±0.05	99.7 ± 0.5
CD8	102.1 ± 2.6	15.3 ± 5.0	2.8±0.02	0.70±0.16	99.9 ± 0.8
CD9	101.6 ± 2.4	15.0 ± 4.9	2.8±0.01	0.65±0.19	100.1 ±0.9

(Where n=3, Mean ± SD)

The batches were made using 3^2 full factorial design in which thickness of all batches were between 2.7±0.06 mm to 2.9±0.05 mm. Hardness of all formulation batches were between 8.3±0.45 kg/cm^2 to 11.3±0.40kg/cm^2 which showed good mechanical strength. Friability of all batches were less than 1%,

hence friability test was passed. The theoretical weight of tablet was 250 mg and weight variation for all batches were in the range of 99.96±0.55 to 101.8±0.32.

% Cumulative Drug Release of Batches CD1 To CD9 Batches 0f Full Factorial Design Batches

Table 19: % Cumulative Drug Release Data of CD1 to CD9 Batches of full factorial design

Time hrs.	CD1 (%)	CD2 (%)	CD3 (%)	CD4 (%)	CD5 (%)	CD6 (%)	CD7 (%)	CD8 (%)	CD9 (%)
Dissolution data in 750 Ml of 0.1M HCl									
1	8.2±0.19	93±0.31	15.1±0.6	16± 0.51	13± 1.43	13± 0.21	9.9± 1.23	10.3± 0.21	9.3 ± 0.35
2	9.5±0.32	16.2±0.23	20.3±0.32	20.1±0.31	23.8±1.31	39.6±0.42	14.2± 254	18..3±0.32	29.7± 0.56
3	15.3±0.4	26.5±0.36	27.3± 1.2	30.3±1.42	33± 1.1	**52.6±0.77**	23.2± 1.9	27.8±1.21	38.6±0.7
Dissolution data in phosphate buffer Ph 6.8 (+ 250 Ml of 0.2 M tri-sodium phosphate)									
4	38.5±1.4	32.2±0.75	32.4± 0.2	36.4±1.21	42.5±2.3	**65.3±1.84**	32.1±0.72	38.5±1.41	48.7±0.53
6	45.6±1.3	42.4±1.58	40.2± 1.1	45.5±0.32	55.3±2.11	**81.5±1.67**	42.3±0.60	43.9±0.55	62.8±0.95
8	57.7±1.2	54.3±1.41	48.5± 1.2	60.6±1.83	66.5±1.21	**92.6±1.21**	48.4±1.67	58.4±1.77	80.4±0.89
12	72.4±1.3	60.5± 1.4	54.6± 0.6	78.5±1.24	84±1.76	**99.3±0.78**	62.7±0.78	63.6±1.01	90.5±0.92
16	78.6±1.5	71.1±1.8	68.1± 0.9	84.4±0.4	98.2±1.07	**99.4±0.71**	66.2±1.40	72.9±0.94	95.5±1.76
20	80.12±1.	80.0± 0.1	72.27±1.7	88.4±0.57	99.5±0.70	**99.5±0.89**	70.6±1.02	80.4±0.88	96.1±0.59
24	82.12±0.	80.7± 0.1	78.2± 1.7	92.4±0.57	99.5±0.70	**99.7±0.89**	78.9±1.02	80.9±0.88	96.82±0.59

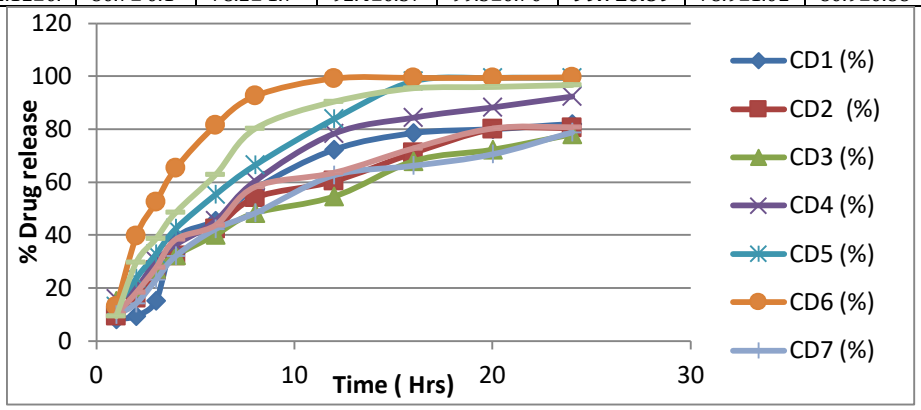

Figure 9: Comparative Dissolution Profile of Formulation Optimization CD1 to CD9

It was observed that as the concentration of osmogene was increasing the drug release also increase and declined beyond certain level of concentration. Combination of Sodium chloride and Potassium Chloride (in the ratio of 1:1) concentration was varied as 25 (CD1, CD4 and CD7), 30 (CD2, CD5 and CD8) and 40 mg (CD3, CD6 and CD9). The cumulative percentage drug release was found to be 82, 80, 78, 92, 99, 99, 78, 80 and 96 respectively for formulation CD1 to CD9 at the end of 24 hrs. Thus, formulation CD6 has showed consistent and efficient drug release over a period of prolonged time and hence same was considered as optimum for the further investigation. For further investigation, CD6 was selected (based on drug release kinetics, Higuchi Matrix correlation).

Model Fitting of *in – vitro* Dissolution data of Self Pore Forming Osmotic Tablet of Carvedilol

Table 20: Model Fitting of *in – vitro* Dissolution data of Self Pore Forming Osmotic Tablet of Carvedilol

Formulation	Zero order Correlation coefficient (R^2)	First order Correlation coefficient (R^2)	Higuchi Matrix Correlation coefficient (R^2)	Korsmeyer – Peppas (R^2)
CD1	0.6995	0.9066	0.9822	0.8980
CD2	0.8994	0.9075	0.9866	0.7972
CD3	0.8996	0.9154	0.9871	0.8978
CD4	0.6998	0.9289	0.9866	0.8998
CD5	0.7405	0.8496	0.9829	0.8854
CD6	**0.8148**	**0.7361**	**0.9922**	**0.9352**
CD7	0.9110	0.8318	0.9051	0.7766
CD8	0.9178	0.8946	0.9023	0.7936
CD9	0.8635	0.8882	0.7834	0.7935

All the formulations were fitted to zero order release, first order release, Higuchi matrix model, and Korsmeyer- peppas model. None of the formulations followed first-order kinetics, which was confirmed by the poor correlation coefficient values. All formulations best fitted both Higuchi matrix model (R^2 =0.9922) and Korsmeyer and Peppas equation (R^2 =0.9352).

Statistical Analysis:

For final optimization, 3^2 full factorial design batches were employed to study the effect of independent variables X1 and X2 on dependent variables drug release at %t50 (Y1) drug release at %t90 (Y2). All the batches were prepared according to the design and analysed using the design expert 13 software. The software suggested respective quadratic model and gave model equation for all dependent variables. The results of ANOVA along with response surface and contour plots were generated for each response which are given in Table and Figure.

Optimization of Formulation Variables

Response 1 - % Drug release at %t_{50}:

% Drug release at %$t_{50}$of CD1 to CD9 batches of carvedilol CPOP tablet was varied from 50.54 % to 71.3 %. Polynomial equation for % Drug release at t_{50} was found to be:

%Drug release at t_{50} = 69.90+2.42A+1.94B-0.5465AB+15.22A^2-1.07B^2

A positive sign for coefficients A and positive sign for coefficient B suggests that as amount of polymer was increased the % drug release was also increased. Contour plot and 3D response surface plots shown in Figure.

Response 1: %drug release at (%t50)

Table 21: Results of ANOVA for % drug release at %t_{50}

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	468.83	5	93.77	44.91	0.0051	significant
A-Amount of osmotic agent	34.61	1	34.61	16.58	0.0267	
B-Amount of sorbitol	22.26	1	22.26	10.66	0.0470	
AB	1.28	1	1.28	0.6154	0.4900	
A^2	352.93	1	352.93	169.03	0.0010	
B^2	1.73	1	1.73	0.8297	0.4295	
Residual	6.26	3	2.09			
Cor Total	475.09	8				

The data of ANOVA Table shows that R^2 and F value of % drug release at t_{50} of the model was found to be 0.9868 and 0.4295, respectively and which imply the model was significant. From the P-values, it was concluded that polymer ratio and effervescent amount had prominent effect (P<0.05) on % drug release at %t_{50}.

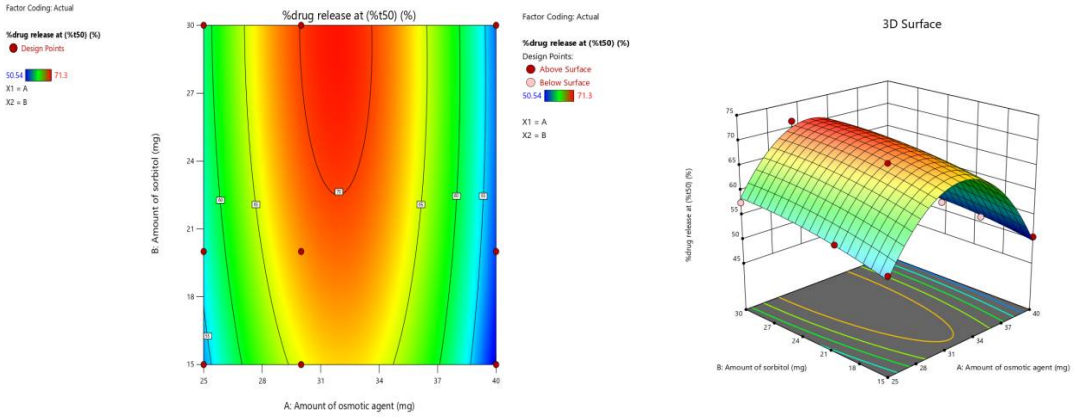

Figure 10: Contour Plot for Effect of osmotic agent(X1) and amount of pore former (X2) on % drug release at %t_{50}

Response 2 -% Drug release at t_{90}:

%Drug release of CD1 to CD9 batches of carvedilol self-pore forming tablet was varied from 84.34 % to 99.7%. Polynomial equation for % drug release at t_{90} was found to be:

%Drug release at t_{90} = 97.83-3.36A+0.6582B+0.6892AB-8.80A^2-0.1038B^2

A negative sign for coefficients A and negative sign for coefficient B suggests that as amount of osmotic agent and amount of pore former was changed from -1 to 1 the % drug release was also increased. Contour plot and 3D response surface plots shown in Figure.

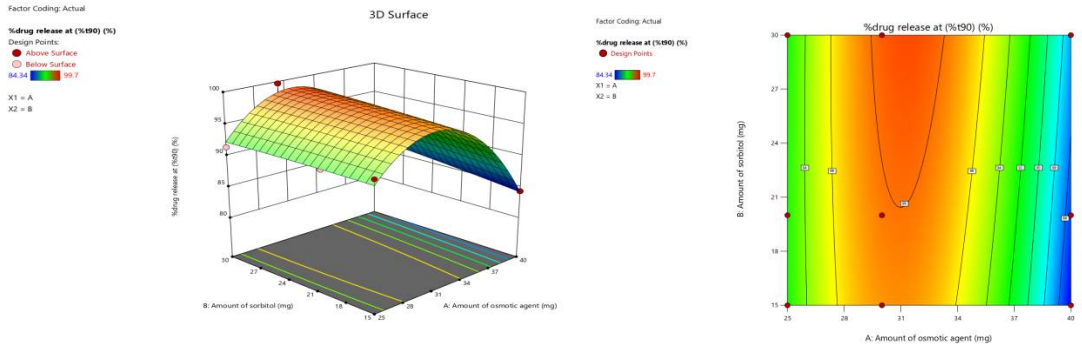

Figure 11: Contour Plot for Effect of amount of osmotic agent(X1) and amount of pore former(X2) on % Cumulative Drug Release at $\%t_{90}$.

Validation of Optimization Design:

Numerical and graphical optimization was performed by using Design Expert software 13 for optimization of final batch control porosity osmotic pump tablet of carvedilol which should have following criteria. Selected criteria for independent and dependent variable for formula optimization:

Independent variables: A. Amount of osmotic agent B. Amount of pore former

Dependent variables: Y1% drug release at $\%t_{50}$Y2 % drug release at $\%t_{90}$

Checkpoint Analysis of Batches CD1 to CD9:

To validate the selected mathematical model, checkpoint analysis was performed and from the overlay plot, two sets of both the independent variables were selected and on the bases of that, one batch was prepared with the quantity selected from the overlay plot. The study was performed for 3 times and obtained actual results mean values of all two dependent variables were compared with predicted values, the differences were found to be significant (P>0.05). Therefore, obtained actual results revealed that the quadric model is valid for relationship between theoretical predictions of dependent variables with the practically obtained results. Overlay plot for combined effect of effect concentration of polymer ratio (X1) and pore former (X2) are shown in Figure.

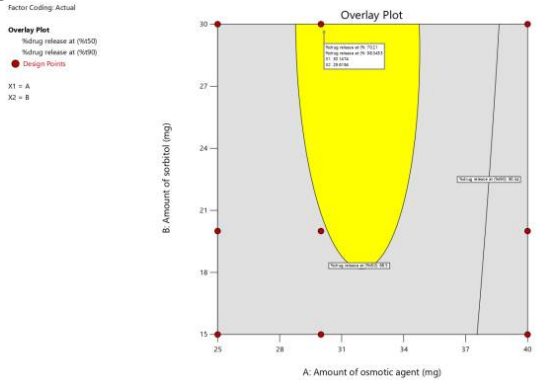

Figure 12: overlay plot of showing combination effect of amount of polymers

The overlay plot reflected that "yellow region" of the area shown in the Figure is the area of interest (experimental region). Formulation having concentration of polymer ratio(X1) and amount of pore former (X2) with % Drug release t_{50}, % Drug release t_{90} was found in experimental region of the overlay plot and having higher desirability than other check point batches. So, it was selected as optimized batch.

Validity of Regression Equations of 3^2Full Factorial Design:

Comparative Table of the observed responses of the predicted responses along with t values are listed in Table 22.

Table 22: Results of Check Point Batch CD6

Batch Code	Parameters	Predicted Value	Experimental Value	t_{cal}	t_{tab}
CD6	% Drug releaset_{50}	44.14	45.12±0.53	1.35	2.015
	% Drug releaset90	90.06	91.67±0.87	1.6	

The results of check point batch revealed that t_{tab} values were found 12.71. Here, t_{cal} value was less than t_{tab} value for all responses at all the levels, which suggest that there was no significant difference between two results. So, equation obtained for selected responses are validated in selected ranges of variables. The close resemblance between the observed and predicted response value assessed the robustness of predictions. These values indicate the validity of generated model.

Optimized Formula of carvedilol self-pore forming tablet

Table 23: Optimized Formula of carvedilol self-pore forming tablet:

Sr. No.	Ingredients	Quantity for 1 tablet
1.	Drug	10 mg
2.	PVP K30	20 mg
3.	NaCl:KCl (1:1)	30 mg
4.	talc	3 mg
5.	Mg stearate	5 mg
6.	Sorbitol	30 mg
7.	Amaranth 3%	1mg
8.	Dicalcium Phosphate	1mg
9.	Total weight	100mg

Result Summary for Carvedilol self-pore forming Tablet of optimized batch CD6

Table24: Result Summary of All Evaluations of Optimized Batch CD6

Results of Optimized Formula		
Sr. No.	**Parameters**	**Result**
1	Angle of repose	29.45±0.59 º
2	Bulk Density	0.62± 0.002 gm/ml
3	Tapped Density	0.73± 0.01gm/ml
4	Hausner Ratio	1.17± 0.01
5	Carr's Index	15.06± 0.14 %
6	Weight Variation	350.40± 0.52 mg
7	Hardness (kg/cm^2)	9.5 ± 0.25 kg/cm^2
8	Thickness (mm)	2.9± 0.03 mm
9	% Friability	0.37±0.03%
13	% Drug Content	99.39±0.22%
14	% Cumulative drug release up to 24hrs.	90.34 %

(Where n=3, Mean ± SD)

Stability Study Data for Optimized Batch CD6:

Table 25: Stability Study Data for Optimized Batch CD6

Sr. No.	Parameters	Storage Period (30 Days) at 30 ± 2 °C Temp. and 65 ± 5 % Relative Humidity
		At30 days
1	Appearance	White powder
2	Drug Content (%)	98.81 ± 0.15
4	% Drug release study	99.82±0.07

(Where n=3, Mean ± SD)

Discussion: Stability study was performed for final optimized CD6 batch. From the stability studies of the optimized formulation for one month, it was found that there was not significant change in appearance, % drug release study and % drug content. No significant change in any of above parameter during storage at 40 ± 2°C temperature and 75 ± 5 % relative humidity indicated that the developed formulation was stable after one month.

CONCLUSION

From the entire study conducted during present investigation can be used to conclude that the developed tablets can be used to treat the hypertension.

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CITATION OF THIS ARTICLE

Rakesh T. Wagh, Rupal K. Jani. Formulation and Characterization of Osmotically Controlled Bilayer Tablets containing Carvedilol as Antihypertensive Drug. Bull. Env. Pharmacol. Life Sci., Vol 11[7] June 2022 : 193-209.

