Design, Characterization and Evaluate Self Pore forming Osmotic Tablet containing combination of Antidiabetic & Antihypertensive Drugs

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Abstract:

Drug candidates having low solubility, shorter biological half life are better candidate for SPFOCDDS formulation. SPFOCDDS can provide continuous delivery of drug at predictable and reproducible kinetics throughout the GIT. Bilayer tablet is new era for successful development of controlled release osmotic tablet formulation along with various features to provide successful drug delivery. Bilayer tablet have been consist of two layers which both are controlled release.

Keywords: Vildagliptin, Carvedilol Phosphate, Osmotic Tablet, CDDS.

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Introduction:

Bilayer tablet offer a possible means of reducing the tablet burden for a patient as it can administer two or added active pharmaceutical ingredients (APIs) in a single fixed dose combination dosage form [1].

In some cases bilayer tablets are designed to overcome chemical incompatibility between two active components. In some chemically sensitive cases an inert layer is added between the two layers to prevent their contact [2].

Bilayer tablets are also developed to achieve a desired drug release profile of the active component present in one layer by utilizing the functional property (hydrostatic and osmotic potential) of other layer. Bilayer tablets can be used to control the delivery rate of one or two different active pharmaceutical ingredients by sandwiching one or two inactive layers, in order to achieve swellable/erodible barriers for modified release [3].

Bilayer tablets offer other advantages like: prolonging the patent life of a drug product, increased efficacy of the active components due to their additive or synergistic effect, reduced toxicity, improved adherence to treatment regimens by patients, convenience of use, and facilitating the logistics of procurement, distribution, and dispensing [4].

The above discussed advantages and capabilities are specific to bilayer tablets that are not achievable by single layer tablets. At the same time there are few disadvantages too during formulation of a bilayer tablet such as,

- Accuracy in weight control of individual layers,
- Delamination/layer-separation during manufacturing, and storage,
- Insufficient tablet breaking force,
- Cross-contamination between the layers (especially for incompatible APIs), and
- Reduced yield.

Diabetes mellitus and hypertension are two universal diseases that frequently coexist [5]. The majority regular cause of death in the diabetic patient is heart illness.

In the present research we had combined Vildagliptin and Carvedilol for better patient compliance. IR layer and controlled layer were prepared separately in previous work. The disintegration and dissolution study of both layers showed optimum release of drugs from both layers.

Selection of Excipients for compression of both layers:

All drug formulations are comprised of 2 elements the API and excipient. API is the active ingredient which is the drug/s and excipients are substances that convey the drug to the recipient. Excipients are synthetically inert substances [6].

Pharmaceutical Excipients are pivotal to the drug formulation industry. An excipient has no therapeutic properties [7]. The standard reason for its existence is to streamline the manufacturing of the formulation and at last encourage physiological ingestion of the medication. Characteristics of excipient play a key role in effecting blending and final product quality [8].

Selecting excipients for tablet manufacturing is a vital process [9]. A precisely picked excipient may lessen manufacturing costs by being multifunctional or may improve user's experience by offering taste veiling properties [10]. An excipient should best suit the planned dose type, the particle sizeofAPIshowawesome flow properties, high density, absorb high moisture and highly hygroscopic [11].

Blend homogeneity can be examined on content uniformity analysis of the API. Getting proper concentration of excipient concentration at appropriate particle size which enhances the flow of API improves tablet manufacturing and has an impact on uniformity of content which helps in attaining the uniformity of blend [12, 13, 14].

Objectives of the Work

- To optimize the bilayer formulation using design of experiment software.
- To perform Drug: Post combination Excipients Compatibility study.
- To formulate and prepare self pore forming osmotic bilayer tablets containing Carvedilol Phosphate and Vildagliptin.
- To achieve greater than 90% drug release after 24 hours.
- To evaluate various pre- and post- compression parameters.
- To conduct accelerated stability studies on the most satisfactory formulation as per ICH guidelines.

Table: LIST OF MATERIALS

Sr. No.	Material	Function	Sources of Material
1.	Vildagliptin	API	**Novartis pharma, Mumbai**
2.	Carvedilol Phosphate	API	Rivera Pharma, Surat, Gujarat
3.	Sodium Chloride	Osmotic agent and Pore-Former	**S.D Fine Chemicals**
4	HPMC	Coating polymer	**S.D Fine Chemicals**
5	Povidone K30	Release retardant	**S.D Fine Chemicals**
6	Magnesium stearate	Lubricant	**S.D Fine Chemicals**
7	Talc	Glidant	**Loba Chemicals**
8	Microcrystalline Cellulose,	Diluent	Loba Chem.

Table: List of Equipment's

S. N	Equipments	Manufacturers
1.	**Digital weighing balance**	**Reptech weighing balance ltd., Ahmadabad**
2.	**Tablet compression machine**	**Multipunch Tablet compression machine, Cadmach machinery Co. Pvt. Ltd, Ahmedabad.**
3.	**Dissolution apparatus**	**Electro lab ltd, Mumbai**
4.	**UV-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., Mumbai.**
8.	**Infrared spectrophotometer**	**Bruker, USA**
9.	**Differential scanning calorimeter**	**DSC TA-60, M/s Shimadzu**
10.	**Tablet Coating Machine**	**Solace Ltd.**

Experimental:

Formulation of bilayer tablet [15, 16, 17]:

Individual layer of both drugs (Vildagliptin and Carvedilol) which was prepared in previous study were considered for the formulation of bilayer tablet. The composition of each layer was shown in following tables.

Table: Layer 1: Composition of Controlled porosity osmotic pump tablet (All values are expressed in mg)

Ingredients	**Formulation code**								
Quantity	VC1	VC2	VC3	VC4	VC5	VC6	**VC7**	VC8	VC9
Vildagliptin	50	50	50	50	50	50	**50**	50	50
Sodium Chloride	10	10	10	20	20	20	**30**	30	30
HPMC EV5	50	75	100	50	75	100	**50**	75	100
PVP 30	10	10	10	10	10	10	**10**	10	10
Pharmatose 200	150	125	100	140	115	90	**130**	105	80
Magnesium Stearate	2	2	2	2	2	2	**2**	2	2
Talc	3	3	3	3	3	3	**3**	3	3
Total Weight(mg)	275	275	275	275	275	275	**275**	275	275

Table: Layer 2: Composition of Controlled porosity osmotic pump tablet as per 32 Full Factorial Design (All values are expressed in mg)

Ingredients	**Formulation Code**								
Quantity	CD1	CD2	CD3	CD4	CD5	**CD6**	CD7	CD8	CD9
Carvedilol	10	10	10	10	10	**10**	10	10	10
PVP K30	30	30	30	30	30	**30**	30	30	30
NaCl : KCl (1:1)	25	30	40	25	30	**40**	25	30	40
talc	3	3	3	3	3	**3**	3	3	3
Mg stearate	5	5	5	5	5	**5**	5	5	5
Eudragit RLPO and RSPO	25	30	40	25	30	**40**	25	30	40
Sorbitol (60% w/w)	15	15	15	20	20	**20**	30	30	30
PEG400	10	10	10	10	10	**10**	10	10	10
Amaranth 3%	Q.S	Q.S	Q.S	Q.S	Q.S	**Q.S**	Q.S	Q.S	Q.S
Dicalicum Phosphate	Q.S	Q.S	Q.S	Q.S	Q.S	**Q.S**	Q.S	Q.S	Q.S
Total Weight(mg)	250	250	250	250	250	**250**	250	250	250

Formulation of bilayer tablet:

Formulations for both layers were given in previous slides. These highlighted formulations were considered for the preparation of bilayer tablet. Prior to compression, lubricated blend of Carvedilol tablets and granules of Vildagliptin tablets were characterized for physical parameters like angle of repose, bulk and tapped densities and % compressibility. The properties of the compressed tablets, such as thickness, hardness, friability, weight variation, and disintegration time were evaluated [18, 19, 20].

Granules of Vildagliptin layers were prepared by slugging method using previously prepared layer for the same. VC7 for Vildagliptin and CD6 for Carvedilol were considered for further investigation and tableting. Both were selected as optimizes based on the release profile observed during the evaluation of individual layer [21].

Formulations for both layers were highlighted in green color in formulation table. These highlighted formulations were considered for the preparation of bilayer tablet.

Ingredients	**Formulation Code**								
Quantity	**CV**	**CV2**	**CV3**	**CV4**	**CV5**	**CV6**	**CV7**	**CV8**	**CV9**
Granules of Vildagliptin	275	275	275	275	275	275	275	275	275
Carvedilol layer	250	250	250	250	250	250	250	250	250
Mg- Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc	00	0.5	1	00	0.5	1	00	0.5	1
Aerosil	00	00	00	0.5	0.5	0.5	1	1	1

Design of Experiment:

3^2 Full-Factorial design [22, 23, 24] was applied to confirm the influence of variables selected.

Design-Expert software 7 (Stat Ease Inc,

Minneapolis, USA) was used [25,26].

Independent variable:

1. The composition of NaCl:KCl (1:1) (X_1)
2. Sorbitol (60% w/w) (X_2).

Variables in coded values are shown in table on next page [27,28]

Dependent variables, first, time for 50% drug release ($t_{50\%}$) and second, time for 90% drug release ($t_{90\%}$).

Both independent variable (X_1 and X_2) were investigated at three levels (i.e.-1, 0, +1). [29,30]

The observed and predicted responses were critically compared [31].

The optimized formulation was selected on the basis of desirability based acceptance criteria and percentage error.

Table: coded values

Factor	Coded Values		
	-1	0	1
X1	25	30	40
X2	15	20	30

Design summary: Design summary was predicted by the design expert software

Design Summary									
Study Type	Factorial		Runs	9					
Initial Design	D-optimal	Coordinate Exchange		Blocks	No Blocks				
Center Points	0								
Design Model	2FI								
Factor	Name	Units	Type	Low Actual	High Actual				
A	Talc	mg	Categoric	0	1	Levels:	3		
B	Aerosil	mg	Categoric	0	1	Levels:	3		
Response	Name	Units	Obs	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio
Y1	CDR	%	9	Factorial	70	100	86.55556	8.538945	1.428571

Method of tablet formation:

Prior to compression, lubricated blend of Carvedilol tablets and granules of Vildagliptin tablets were characterized for physical parameters like angle of repose, bulk and tapped densities and % compressibility. The properties of the compressed tablets, such as thickness, hardness, friability, weight variation, and disintegration time were evaluated. Granules of Vildagliptin layer were prepared by slugging method [32,33, 34] using previously prepared layer for the same.

Formulations for both layers were given in previous slides. These highlighted formulations were considered for the preparation of bilayered tablet. Prior to compression, lubricated blend of Carvedilol tablets and granules of Vildagliptin tablets were characterized for physical parameters like angle of repose, bulk and tapped densities and % compressibility. The properties of the compressed tablets, such as thickness, hardness, friability, weight variation, and disintegration time were evaluated [35, 36, 37, 38]. Granules of Vildagliptin layers were prepared by slugging method using previously prepared layer for the same. V7 for Vildagliptin and C6 for Carvedilol was consideredforfurther investigation and tabletting. Both were selected as optimizes based on the release profile observed during the evaluation of individual layer.

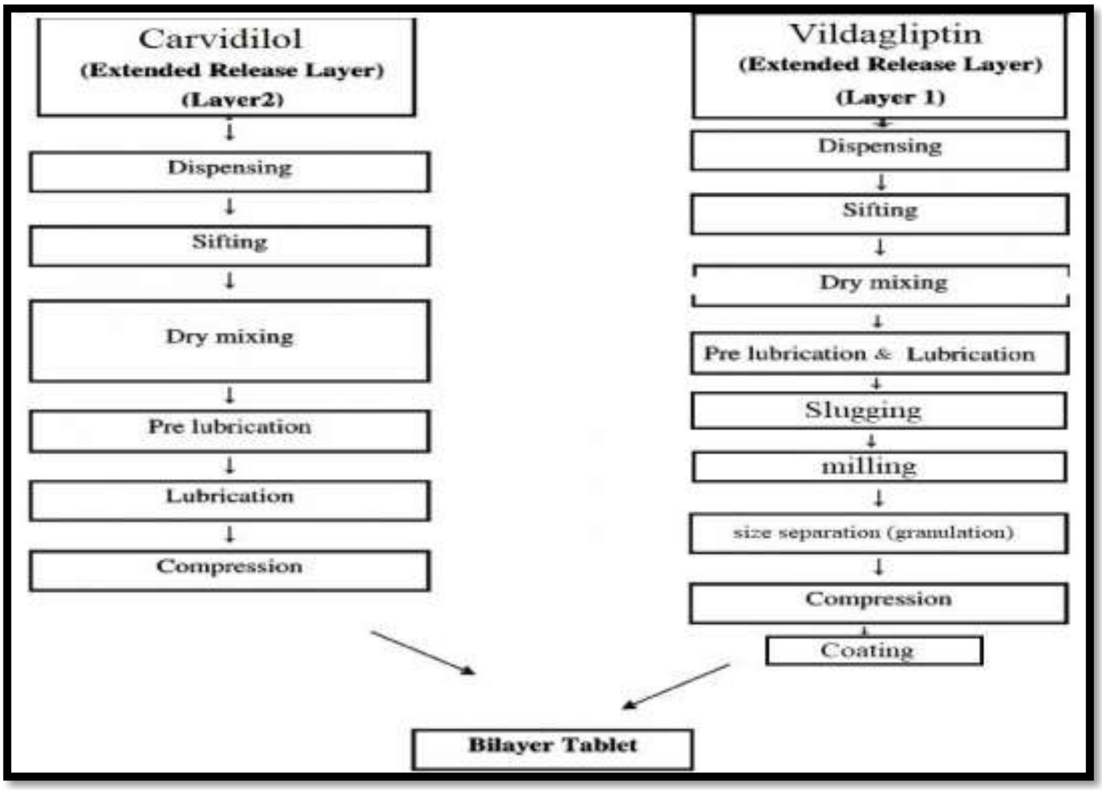


Figure: bilayer tablet formulation process.

Coating -

Required qty. of Eudragit RLPO and RSPO were dissolved in sufficient amount of isopropyl alcohol: acetone (30:70) at 40° in a water bath.

Sufficient amount of plasticizers like PEG400 was added [39].

Aqueous pore forming agent (60% w/w sorbitol) was dispersed in methanol and added to solution of Eudragit polymers with Amaranth 3% as coloring agent[40].

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 24h.

Evaluation of bilayer tablets:

Precompression evaluation parameters [41, 42, 43]:

Angle of repose:

Angle of repose is defined as the maximum angle viable between the surface of a pile of the powder and horizontal aircraft. The frictional pressure in a unfastened powder or granules can be measured by using angle of repose.

$\tan \Theta = h/r$

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

Where,

Θ: is the angle of repose h is height of pile

R: is radius of the base of pile

Different ranges of flowability in terms of angle of repose are given in following Table

TABLE: angles of reposes and flow properties

Angle of Repose (degrees)	**Flow**
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Procedure:

A funnel filled with sample to the brim. Then the sample allowed wafting easily through the orifice under the influence of gravity force. Granule pile was allowed to form till to touch the tip if funnel. Gliding capability of the granule samples was determined from the diameter of the hip formed at the base and the height of the pile.

Bulk density:

Bulk density is described as the mass of a powder divided via bulk volume. the majority density of a powder relies upon primarily on particle size and length distribution, particle shape, and the affinity of the particle to stick to each other.

Procedure:

Loose Bulk density (LBD) and the tapped bulk density (TBD) were determined using densitometer. Suitable quantity of sample powder was taken which was previously passed through the standard sieve. A sample free from the agglomerate was introduced into a 25ml Measuring cylinder. Density apparatus was allowed to run either 100 tappings or kept on for 5 min in order to record the data. LBD and TBD were calculated using following formula;

TBD=Weight of powder/ Volume of packing LBD=

Weight of powder/ Tapped packing **True density**

True density of granules is carried out by using specific gravity bottle:

Method followed was,

Taken weight of the empty bottle i.e. W1

Then added 3/4th of liquid in it, and weighed which was W2

Then added 1/4th quantity of powder then weighted again, which was W3

Finally taken the weight of bottle plus powder and liquid which was considered as W4

Formula used was, : (W3 – W1)

True density = (W2 – W4) (W1 – W3)/ρ

Percentage Porosity

This can be calculated by taking the value of bulk density and true density

Percent Porosity = 1- Bulk density X 100/ True density

Quality control tests for in process and finished tablets were done, they are thickness of tablet, weight variation of tablets, friability of the tablets, assay etc. Weight variation test: it a in process quality control test conducted for tablets to monitor any fluctuations in weight of the tablets, if any major fluctuations are observed adjustment of compression parameters are made. To conduct or check uniformity of weight twenty tablets are randomly picked from the batch during compression and their individual weights are measured and total weight of all twenty tablets were calculated. Total weight is divided with twenty tablets to get average weight. Now individual weight of each tablet is compared with average of total twenty tablets. Each tablet should not deviate not more or less than five percent of the average value. The percent deviation was calculated using the following formula.

Compressibility Index:

The Carr index (also: Carr's index or Carr's Compressibility Index) is a sign of the compressibility of a powder. It is named after the researcher Ralph J Carr, Jr.

The Carr index was calculated by following formula,

$$C = 100\frac{\rho_T - \rho_B}{\rho_T}$$

Where ρBis the freely settled bulk density of powder sample, and ρT is tapped bulk density of powder after "tapping down". It can also expressed as

$$C = 100(1 - \rho_B/\rho_T)$$

The Carr index is regularly used in pharmaceutics as assign of the compressibility of powder/granules. In a free-flowing powder, the bulk density and tapped density would be close in value; therefore, the Carr index would be small. On the other hand, in a poor-flowing powder where there are greater inters particle interactions, the difference between the bulk and tapped density observed would be greater; therefore, the Carr index would be larger. A Carr index more than 24/25 is considered to be asign of poor flowability, and less than 15 is a sign of good flowability. Another way to measure the flow of a powder is the Hausner ratio,

Hausner ratio:

The Hausner ratio is number that is correlated to the flowability of a powder or granular powder sample material. It is named after the engineer Henry H. Hausner, 1900 to 1995.

The Hausner ratio is calculated by the formula

$$H = \frac{\rho_T}{\rho_B}$$

Where,

ρB : freely settled bulk density of the powder, and

ρT : tapped bulk density of the powder.

The Hausner ratio is not an absolute possession of a material; its value can vary depending on methodology used to determine it. The Hausner ratio is used in a extensive variety of industries as an indication of the flowability of a powder. A Hausner ratio greater than 1.25 - 1.4 is considered to be an indication of poor flowability.

Both the Hausner ratio and the Carr index are sometimes criticized, despite their relationships to flowability being established empirically, as not having a strong theoretical basis. Use of these measures persists, however, because the equipment required to perform the analysis is relatively cheap and the technique is easy to learn.

Post compression evaluation parameters:

Physical Parameters:

Size and shape: The tablets formulated were circular in shape with 8 mm diameter

Organoleptic Characters

Colour: bilayer tablet one of layers has pink and other has white color.

Figure: Physical appearance of the tablet prepared during investigation

Test for hardness of tablets:

It is a diametrical crushing strength and forces which is required to break the tablets. Strength of any tablet dosage form indicates its mechanical and tensile strength. The hardness of tablet may be change depending on the inactive ingredients used type of tablet. Hardness measured in units of kilopascals and tested by Schleuniger tester. "Hardness factor". Tablet hardness testing, is a lab technique used by the pharma industry to establish the breaking end and structural reliability of a tablet and discover out how tablet changes "under condition of storage, transport, packing and handling prior to use". The breaking end of a tablet is based on shape. It is alike to friability test.

Tablet hardness testers original appeared in the 1931s. In the 1952s, the Strong Cobb tester was used. It was patented by Robert A. on July 22, 1952.

There are 2 major processes to check tablet hard ness: compression testing and three points bend testing. For compression testing, the analyst usually aligns the tablet in a repeatable way, and the tablet squeezed amid a fixed and moving jaw. The first machines recurrently applied force with a spring and screw thread until tablet start to break. When the tablet fractured, hardness is recorded on sliding scale.

Figure: lab scale hardness tester

Figure: Industrial scale/digital hardness tester

Friability test:

Friability is the process of quality control tests conducted to check the amount of tablets loses their weight when they are allowed for friability [44]. Tablets to withstand adhesions, shock when they were allowed to and during transportation when packed in container or other suitable packaging materials. Process of friability is done by Roche Friabilator. It was rotated at a rate of 25 rpm. Ten tablets were weighed collectively and placed in the chamber of the Friabilator [45]. It consists of rotating drum where tablets are placed and allowed to rotate and make tablets to fall from 6 inches height in the chamber for 4 minutes where 100 rotations made. Initial weight and final weight of the tablets were noted and percent of weight lose was determined [46]. Maximum percent weight loss allowed is up to 1% and calculated using the formula.

Active content ingredients (assay): The amount of active ingredient(s) was determined and compared with standards stated in the monograph. Twenty tablets were used for assay. All the batches should fall within the limit of 95– 105 %.

Uniformity of content: Twenty tablets are crushed in mortar after randomly selected from batch. Then, powder is placed in twenty flasks volumetric and volume is made up with pH 6.8 phosphate buffer. The content was shaken well for some time and kept for 30 minutes for dissolving of drug completely. The mixtures were filtered and appropriate dilutions were made. Drug content is determined at l max 233 nm against blank reference in case of

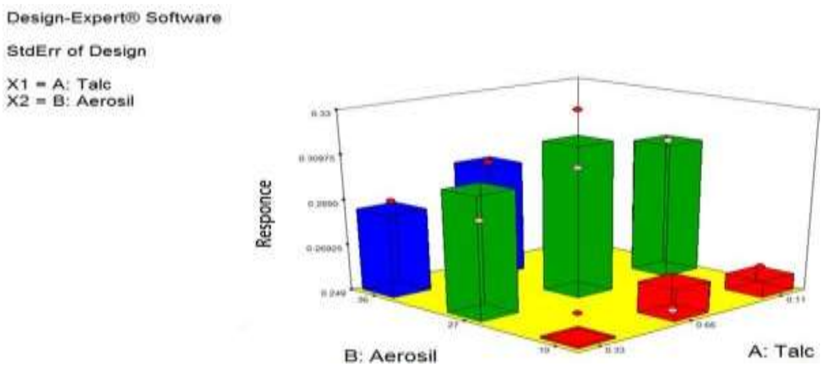
Drug release studies [47, 48, 49]: release of drug in-vitro conditions was carried out in dissolution apparatus of USP type two a paddle one. Medium of dissolution was taken is purified 900ml of water. Dissolution flak is kept in water bath maintained at body temperature around thirty seven degrees centigrade. Rotation of shaft was kept for 75 rpm and 100 rpm for metformin and glimepiride respectively. Tablets are place in basket of dissolution apparatus and allowed to run for 24 hrs for the tablet. Aliquots are collected of 10ml for every specified time using pipette sampler and aliquots are collected of 10ml for every specified time intervals. Each collected sample is filtered through 10 micrometer filter. A fresh medium of dissolution is replaced after taking out each sample, the collected samples are made to dilute to required concentrations and analyzed for drug content at each time intervals using U.V spectroscopy.

Accelerated stability studies [50, 51]:

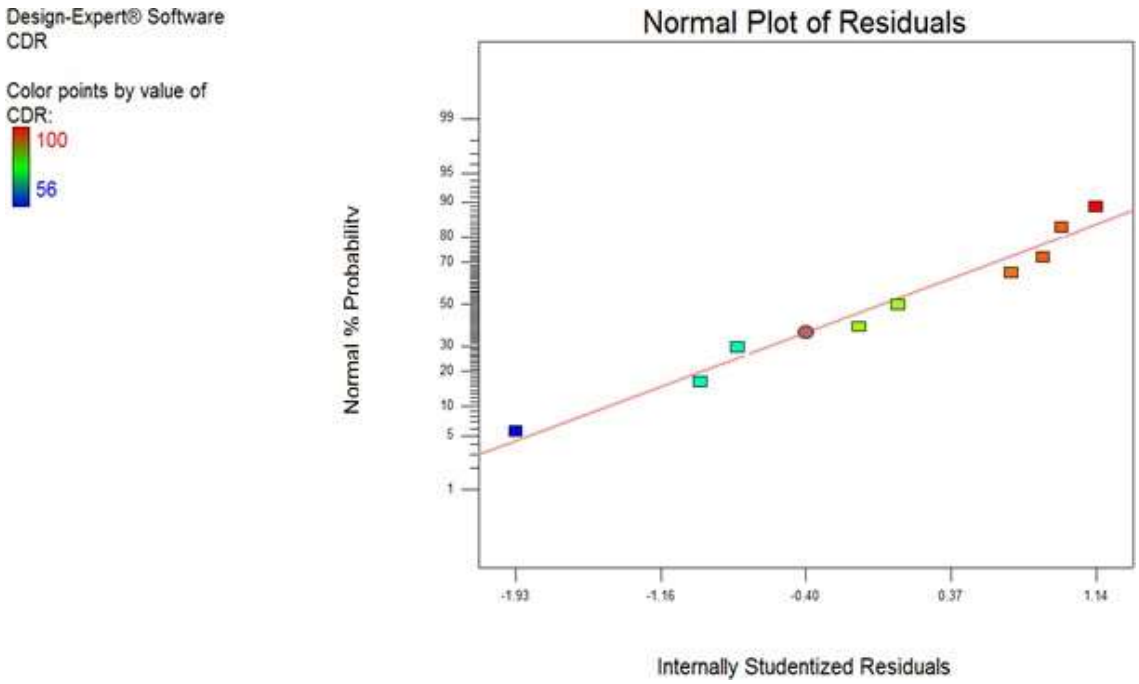
Bilayer tablets (batch) were packed in 90 gsm thick aluminum foil strips laminated with PVC. Tablets are exposed to different environmental conditions of temperatures and humidity for one month by placing in stability chamber, the conditions are 40ºC and 75% RH and 60ºC during one month period. Tablets are collected after one month and drug content is determined.

Result and discussions:

Design of experiment:



3 D response surface showed that there is significant effect of X2 (concentration of aerosol) on selected response. Two excipients, aerosol and talc were used in present investigation. To investigate the effect of these excipients, response selected was the drug release. 3D response revealed that the aerosol has got prominent effect on the response than that of talc. This was owing to the difference in hrophilicity of both expients. Literature review done for the further investigation showed that the aerosol is hydrophilic and talc is hydrophobic [52] (https://doi.org/10.1016/B978-0-12-802786- 8.00013-9). Because of this difference in hydrophillicity, the excipient which is more hydrophilic can affect the drug solubility and consequently drug release. In present investigation aerosol has shown expected drug release pattern. This study revealed that the aerosol was adequate excipient which may affect positively drugrelease.



In statistical applications, a studentized residual is quotient resulting from division of a residual by an estimate of its standard deviation. It is a form of a Student's t-statistic, with the estimate of error varying between points. This is an imperative technique in the recognition of outliers. It is amid several named in honor of William S. Gosset, who wrote under pseudonym Student. Dividing a statistic by a sample standard deviation is called studentizing, in analogy with standardizing and normalizing.

T-statistic is ratio of departure of the estimated value of a parameter from its hypothesized value to its std error. It was used in hypothesis testing via Student's t-test. The t-statistic was used in a t-test to determine whether to support or reject the null hypothesis. It was very similar to the Z-score but with the difference that t-statistic was used when the sample size was small or the population standard deviation was unknown. For example, the t-statistic was used in estimating population mean from a sampling distribution of sample means if the population standard deviation was not known. It was also used alongside with p- value when running hypothesis tests where the p-value tells what odds are of the results to have happened. In present investigation, predicted points were along side of the regression line and support the validity of model used during application of design of experiment. Plot of internally studentized residuals was shown in above figure.

Response	1 CDR				
ANOVA for selected factorial model					
Analysis of variance table [Partial sum of squares - Type III]					
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	0	0		0.0012	0.0012
Residual	45	8	82.02778		
Cor Total	43	8			
Values of "Prob > F" less than 0.0500 indicate model terms are significant.					
In this case there are significant model terms.					
Values greater than 0.1000 indicate the model terms are not significant.					
If there are many insignificant model terms (not counting those required to support hierarchy model reduction may improve your model.					
Std. Dev.	9.056919		R-Squarec	9.1	
Mean	86.55556		Adj R-Squ	9.6	
C.V. %	10.46371		Pred R-Sq	-0.26563	
PRESS	830.5313		Adeq Prec		
A negative "Pred R-Squared" implies that the overall mean is a better predictor of your response than the current model.					
Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High
Intercept	86.55556	1	3.018973	79.59379	93.51732
Final Equation in Terms of Coded Factors:					
	CDR	=			
	86.55556				
Final Equation in Terms of Actual Factors:					
	CDR	=			
	86.55556				

ANOVA reveals that the model used was significant and talc at higher level and aerosol at middle level shows the better interaction effect. The predicted model by design expert is valid enough and also supported with the %CDR found during release study. A validating experiment was also conducted to verify the design space suggested by the software. A validating experiment revealed the fitness of the model selected for the resent investigation.

Precompression evaluation Parameters:

Table: Evaluation of Precompression Parameter of Self Pore Forming Osmotic Controlled Release bilayer Tablet

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
CV1	28.28±0.521	0.49±0.027	0.58±0.023	11.97	1.18
CV2	27.9±1.99	0.52±0.024	0.58±0.019	12.96	1.11
CV3	27.52±1.24	0.54±0.036	0.61±0.015	12.03	1.11
CV4	28.41±0.908	0.51±0.031	0.60±0.022	11.81	1.16
CV5	27.47±0.43	0.52±0.025	0.61±0.013	12.63	1.18
CV6	27.83±0.168	0.51±0.012	0.58±0.026	11.55	1.15
CV7	28.28±0.521	0.49±0.027	0.54±0.023	12.52	1.18
CV8	28.28±0.521	0.49±0.027	0.58±0.023	11.91	1.18
CV9	24.19±1.99	0.52±0.024	0.58±0.019	12.96	1.11

The powder blends of formulations CV1 to CV9 have the bulk density ranged from 0.49±0.027 to 0.52±0.024 and tapped density from 0.58±0.023 to 0.61±0.013. The compressibility index values less than ten, 11 to 15, 16 to 20, 21 to 25, 26 to 31,
32 to 37 and greater than 37 indicates excellent, good, fair, feasible, poor, very poor and very poor flow respectively and powder blends of all the formulations [CV1 to CV9] developed in the formulation development phase were found to be possessing the good to fair flowability i.e. Approx. 11 to 15 %. CV6 has shown the least value of an index (11.52). The ideal Hausner's ratio values of 1.0- 1.11, 1.12-1.18, 1.19-1.25, 1.26-1.34, 1.35-
1.45, 1.46-1.59 and greater 1.60 indicates excellent, good, fair, possible, poor, very poor and very poor flow respectively and powder blends of all the formulations were found to be possessing the fair to passable flowability i.e. 1.11 to 1.18. The ideal angle of repose values of less than 25, 25-30, 30-40 and greater than 40 indicates excellent, good, passable and very poor respectively and the experimental values of all the formulations were ranged from 24 to 27 indicates good to passable flowability. From the studies conducted for pregranulation stage, it may be concluded that the CV6 formulation has shown optimum flow characteristics which are essential for the compression.

Evaluation of post compression parameter:

Post compression evaluation parameters revealed that the formulation code CV6 may have all necessary parameters to be as an effective drug delivery system. Other drug dose formulations also have adequate outcomes. Further, results from the

Table: Evaluation of post compression parameter of self pore forming Osmotic Tablet

Formulation Code	Hardness kg/cm²*	Friability (%)	Uniformity of Weight (per 1000 mg)	Assay (%) (MH)	Thickness (mm)*
CV1	7.9±0.3	0.96	952±2.93	98.9	7.0±0.12
CV2	8.1±0.4	0.88	950±3.09	99.6	6.8±0.11
CV3	8.0±0.2	0.96	951±2.04	100.22	6.8±0.13
CV4	7.0±0.5	0.87	952±1.92	103.92	6.8± 0.11
CV5	7.6±0.3	0.96	950±1.72	104.74	6.9±0.114
CV6	7.8±0.6	0.98	951±2.02	100.83	7.0±0.11
CV7	7.0±0.1	0.88	951±1.92	101.92	6.8± 0.10
CV8	7.5±0.1	0.8	952±1.72	105.74	6.9±0.14
CV9	7.0±0.5	0.7	941±2.02	101.63	7.0±0.12

Results from the optimization (using DOE) support that formulation code CV6 may be an effective drug dose formulation as compared to the other formulations. Hardness (kg/cm2), Friability (%), Uniformity of Weight (per 1000 mg), Assay (%)(MH), Thickness (mm) of the optimum formulation (CV6) was found to be 7.8±0.6,0.98, 951±2.02, 100.83, 7.0±0.11 respectively.

DISSOLUTION STUDY OF TABLETS:

- The release rate was determined using United State Pharmacopoeia (USP) **XXIV dissolution testing apparatus II (paddle method).**
- For dissolution 3 tablets of each batch were subjected to the study and mean value was considered as % drug release.

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Mr. Rakesh T. Wagh, Dr. Rupal K. Jani/ Design, Characterization and Evaluate Self Pore forming Osmotic Tablet containing combination of Antidiabetic & Antihypertensive Drugs

- The dissolution test was performed using 900 ml of **0.1N HCl pH 1.2 followed by pH 6.8 phosphate buffer** as dissolution medium, at 37 ± 0.5°C and 50 rpm.
- A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at **0, 3, 6, 9, 12 hours.**
- The samples were filtered through a 0.45 micron membranefilter.
- Absorbance of these solutions was measured at 238 nm using a Shimadzu spectrophotometer.
- Cumulative percentage of drug release was calculated using an equation obtained from a standard curve both drugs were evaluated using UV Visible spectroscopic method and the average of both are considered for the release studies.

Table: In vitro drug release profile

Time hrs.	**CV1 (%)**	**CV2 (%)**	**CV3 (%)**	**CV4 (%)**	**CV5 (%)**	**CV6 (%)**	**CV7 (%)**	**CV8 (%)**	**CV9 (%)**
0	0.00	0.00	0.00	0.00	0.00	**0.00**	0.00	0.00	0.00
3	43.93 ±1.12	20.95 ±1.05	41.38 ±1.89	49.37 ±1.83	47.85 ±0.94	**24 ±1.42**	26.95 ±1.05	21.38 ±1.89	39.37 ±1.83
6	50.31±0 .89	41.15±0 .92	45.72±1 .37	56.61±1 .63	52.69±1 .14	**49.82±1 .53**	40.15±0 .92	55.72±1 .37	66.61±1 .63
9	80.43±0 .98	60.04±1 .13	83.17±1 .83	70.32±1 .51	72.02±1 .06	**84±1.87**	70.04±1 .13	73.17±1 .83	80.32±1 .51
12	89.95±1 .33	81 ±1.07	90 ±1.53	89 ±1.46	85±0.56	**100.49 ±1.74**	80 ±1.07	80 ±1.53	80.9 ±1.46

Above table shows dissolution profile for batch CV1-CV9. All formulations have shown drug release from the formulations. The pattern which shows more controlled release over a period of stipulated time was considered as the optimum one. Drug release study for CV1 to CV3 for Carvedilol was observed in an unusual way. CV6 was considered as the optimized one because of more controlled release of both actives.

In rest of formulations drug release was optimum for initial 2 hrs then it was found to be consistent for further 12 hrs. it may be concluded that the osmotic drug delivery technology used in present formulation was optimally delivering the active ingredients and successfully used for the development of drug delivery.

Formulation CV7 to CV9 were not considered for the release study as the %CDR was quite inappropriate for the said formulations.

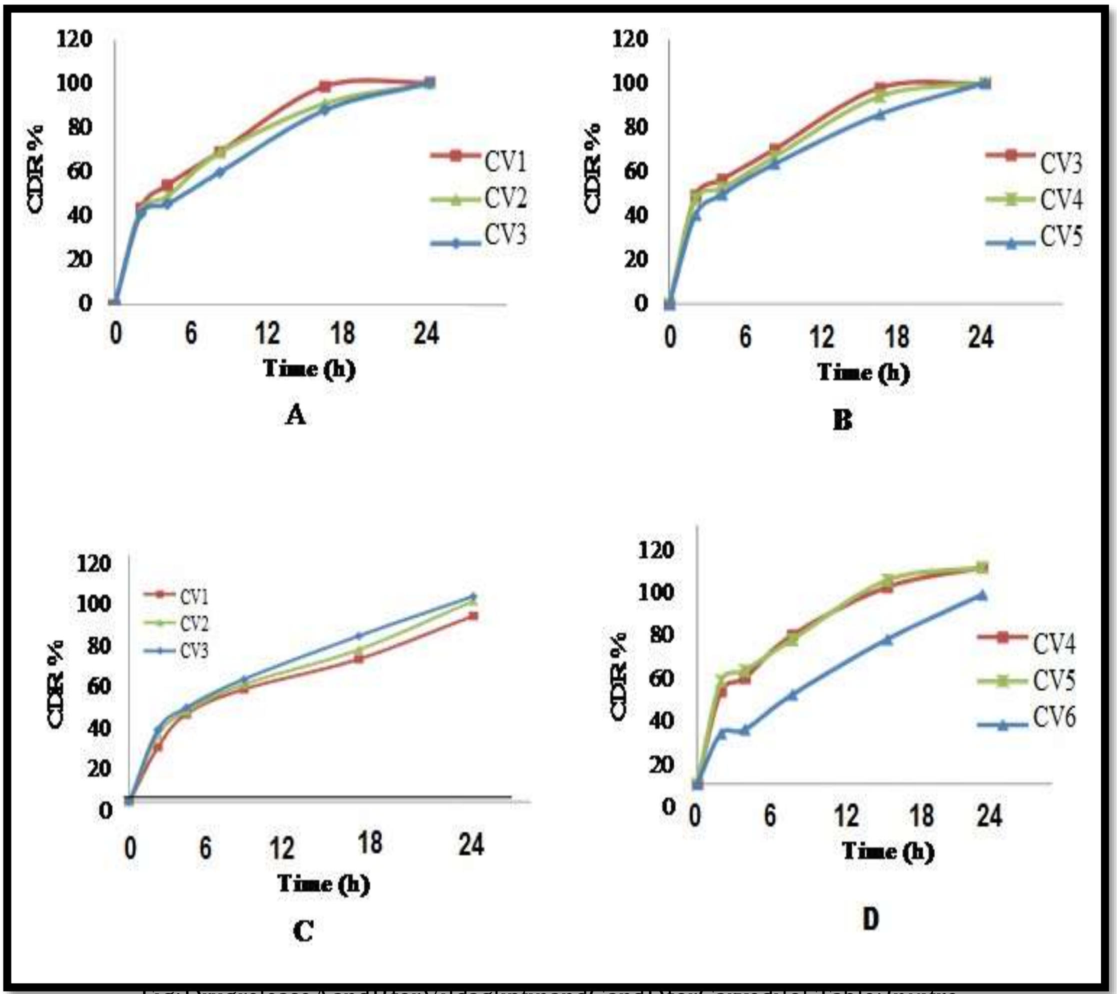

Fig:DrugreleaseAandBforVildagliptinandCandDforCarvedilol Table:*In vitro*

releasein6.8bufferofphosphateRegressionequations

Sr. No.	***In vitro* release in 6.8 buffer of phosphate Regression equations**			
	Zero Order	I^{st} order	Higuchi model	Korsemeyer- Peppas model
01	y = -7.6552x + 83.207 R^2 = 0.9029	Log y = -0.1575x + 2.1398 R^2 = 0.9165	y = 27.26x + 6.6027 R^2 = 0.9923	y = 0.4659x + 1.5052 R^2 = 0.9921
02	y = -7.4181x + 80.974 R^2 = 0.8662	Log y = -0.1244x + 2.0355 R^2 = 0.9871	y = 28.679x +3.9287 R^2 = 0.9803	y = 0.4255x + 1.5479 R^2 = 0.9673

- The results of dissolution data fitted to various drug release kinetic equations. Higuchi model was found to be the best fitted in all dissolution profile having higher correlation coefficient 0.992 followed by Peppas model and first order release equation.

- Slope of Korsemeyer-Peppas model equation indicates type of release phenomena involved. The 'n' value could be used to characterize different release mechanisms as shown in Table. Slope obtained is less then 0.5, hence Metformin release mechanism might be Fickian diffusion.

Table: Slope of Korsemeyer-Peppas equation and proposed mechanism of drug release

Slope (n)	**Drug Release Mechanism**
<0.5	Fickian Diffusion (Higuchi Matrix)
0.5 < n < 1	Non- Fickian diffusion
1	Case II transport

Stability Study:

In this work, selected formulation was stored at 40° C / 75 % RH and 60°C, 80 % RH for one month and in vitro release studies were carried out further. The stability data acquired during investigation revealed that the formulations were stable at an accelerated conditions (accelerated stability study) for one month at 40° C / 75 % RH and 60°C / 80 % RH. The results are mentioned in the following Table and figure.

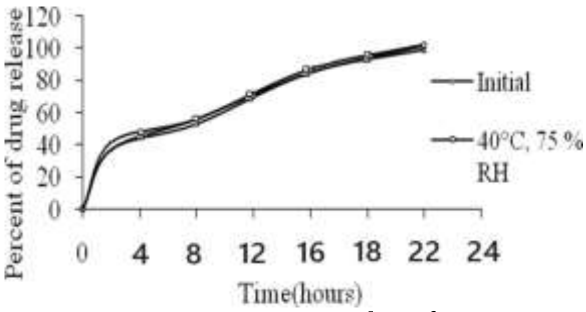

Figure: Comparison average release from Formulation of initial and accelerated stability condition after one month storage

Table: Average Dissolution profile for bilayer tablet of initial, one-month 40° 75RH and 60°C, 80%RH

***Cumulative Percentage of Drug release AM ± SD**			
Time in hrs	**Initial**	**40°C 75% RH**	**60°C 80% RH**
0	0	0	0
4	41±1	42±1	41±1
8	56±1.0	56±1.0	53±1.5
12	64±1.5	65±1.0	64±1.0
16	85±1.5	87±1.0	85±1.0
18	89±1.5	90±1.0	91±1.0
20	89±1.0	90±1.5	92±1.0
22	101±1.0	102±1.5	99±1.0

Result and Conclusions:

Drug candidates having low solubility, shorter biological half life are better candidate for SPFOCDDS formulation. SPFOCDDS can provide continuous delivery of drug at predictable and reproducible kinetics throughout the GIT.

Pharmaceutical active ingredients can be delivered in a controlled manner over longer period by osmotic pressure.

Using above mentioned background, SPFOCDDS was developed successfully in present investigation.

In the present investigation, following attempts have been made successfully,

Formulation, optimization & evaluation of combination of antihypertensive & Antidiabetic drug.

In present study, Preformulation protocol was performed successfully to determine physicochemical characteristics of drug and drug dose formulation. Same study was also used to determine incompatibility between actives and excipients. Preformulation study for drugs, Carvedilol and Vildagliptin revealed that the drugs used in present investigation are compatible with all excipients used during formulation development.

- Formulation for both layers was developed successfully using design of experiments. Data analysis and statistical significance was determined successfully which revealed that the variables and models selected during study were significant.
- Both layers have shown drug release pattern as per the disease treatment protocol requirement.
- After formulation of both layers, a bilayer tablet was developed successfully which also shown an excellent drug delivery pattern over a period of stipulated time.
- Stability study protocol was also studied for the prepared formulation. Stability study also shown that the formulation was found to be stable during the stipulated study period. Accelerated stability study protocol was followed during the study.
- From the entire study conducted during present investigation can be used to conclude that the SPFOCDDS developed might be used to treat the diabetic hypertension. Moreover, study conducted during present investigation may also contribute to scientific community as well as social community.

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