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Development And In Vitro Evalaution Of Acarbose Osmotic Tablets Using Box-Behnken Design Approach

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Abstract
The present research work was aimed to develop an osmotic drug delivery system at a controlled rate for an antidiabetic drug, acarbose. The formulations/tablets were composed of acarbose drug surrounded by microporous film containing cellulose-acetate phthalate (bio-compatible polymer) along with water soluble pore forming agent polyethylene glycol. The osmotic tablets were formulated employing wet granulation technique and statistically optimized via Box-Behnken experimental design approach utilizing design expert 360 version 12.0. These tablets were characterized for before and after compression parameters. Effect of three independent variables i.e. NaCl as an osmotic agent, PVP K30 as binder as well as film forming agent and Microcrystalline cellulose (MCC) as binder was evaluated on % drug release at 16th hrs and % swelling index. High swelling index was observed in the optimized formulation F10 (135±0.23%) exhibiting cumulative drug release of 75.46% at 16th hrs. The significant results were obtained after fitting acquired data in ANOVA. Optimized batch also exhibited controlled release of drug over 24 hrs as it was found to follow zero order drug release kinetics. Stability studies indicated that all optimized formulations proved stable as evidenced by negligible change in drug content and other parameters over the time. These findings suggest that the formulated osmotic tablet loaded with acarbose have proved to be good formulations and would be proved effective for the treatment of diabetes mellitus.
Keywords*: Optimization, Box-Behnken design, drug release, osmotic tablets, in vitro, pharmacokinetic*

INTRODUCTION

As conventional drug delivery system has not any check on liberation of drug and its therapeutic potential on the distinct location, therefore, now a days, the focus of researchers is towards development of novel-drug-delivery-system[1]. Depending upon different physiological components such as state of stomach before and after taking meal, gastrointestinal tract pH, gastrointestinal movement, rate as well as extent of drug's absorption is found to be varied from conventional dosage forms. The type of dosing pattern followed by conventional drug delivery system may result in fluctuating and unpredictable plasma concentration, so, there is need of controlled release formulations which provides effective concentration at target site and minimize drug fluctuation in plasma. The above mentioned disadvantages can be overcome by a practical approach known as osmotic drug delivery system (ODDS), where drugs can be delivered for a prolonged time period in a controlled fashion following the principle of osmosis. ODDS have acquired great attention in the last two decades for being preferred among the various drug-delivery system to deliver the active ingredient in a controlled way. Number of patents and research articles for elementary-osmotic pump, push-pull osmotic pump and controlled-porosity osmotic pump (CPOP) are available[2,3]. Novel method of drug-delivery i.e. osmotic pump systems offers some special characteristics such as controlling the concentration of drug to targeted tissues, prolonging time period of drug's therapeutic potential, drug-release-kinetics at zero-order and equivalent in vitro, in vivo drug release pattern. Semipermeable membrane coating along with hydrophillic material responsible for pore formation encircles osmotic core containing active pharmaceutical ingredient and an osmogen. When it comes in proximity to media, the agents responsible for pore formation get dissolved and in situ microporous membrane formation takes place that is water permeable. Hence, drug gets in dissolved forms. Drug release from this system is dependent upon semipermeable membrane's thickness,

quantity of porosity causing agent and difference in osmotic-pressure produced across semipermeable membrane[4, 5]. Acarbose, an intestinal alpha glucosidase inhibitor, possess a great inhibition against sucrose and employed in treatment of diabetes mellitus type II. The normal dose of acarbose for the treatment of hyperglycemia is 25 mg exceeding to 100 mg thrice a day and available in market as 25, 50 and 100 mg tablets. They have much reduced systemic bioavailability owing to that found to possess less side effects compared to contemporary anti-diabetic drugs. Biological half-life of acarbose is 2 h[6]. Osmotic tablets of acarbose with controlled porosity have been formulated, optimized and evaluated in the present study to maintain plasma concentration of drug in a better way having programmed release pattern. The present research is aimed to optimize osmotic tablets of antidiabetic drug having great therapeutic potential which release the enclosed drug in controlled manner.

MATERIALS AND METHODS

A gift sample of acarbose was obtained from Innova captab, Baddi, Himachal Pradesh, India. Cellulose acetate phthalate was procured through Yarrow Chem Product, Mumbai, India. Mannitol, magnesium-stearate, isopropyl alcohol and talc were acquired from S.D. Fine Chem Limited, Mumbai, India. Microcrystalline cellulose, PEG 4000 along with PVP K30 were procured from Loba Chemie, Mumbai, India. Analytical grade's chemicals were utilized throughout the experiment.

METHODOLOGY

Identification of pure drug (acarbose)

The acquired sample of drug of acarbose was identified by FTIR and determination of melting point. Solubility was also determined of this drug sample. The data was compared with reference spectrum of drug as provided in Indian Pharmacopoeia and solubility data has already been given in our previous research paper [7].

Percentage assay determination of Acarbose by HPLC

HPLC was employed to identify the obtained sample of drug by doing its assay. Assay of working standard solutions of acquired drug sample was performed.

Box Behnken Design (BBD) experiment for osmotic tablets' optimization

Optimized acarbose loaded osmotic tablets were obtained after applying Box-Behnken design using response surface methodology (Design Expert® Software-Version 12)[8].

Independent variables included NaCl concentration (X_1), PVPK30 concentration (X_2), and MCC concentration (X_3) at three grades such as low, medium as well as high for preparation of fifteen formulations. These chosen variables were studied with respect to these responses i.e. % drug release at 16th hrs (Y_1) and % swelling index (Y_2) as presented in Table 1. In addition to this, 3D, response-surface graphs and contour plots were drawn to represent influence of predetermined parameters on the acquired responses..

Table 1: Vraious independent variables in Box–Behnken design

Factor	**Independent variables**	**Unit**	**Low**	**Medium**	**High**
X_1	NaCl	mg	30	35	40
X_2	PVPK30	%w/w	2	3	4
X_3	MCC	mg	50	60	70
Sr. No.	**Response**	**Goal**			
1	% Drug Release at 16th hrs	Maximize			
2	% Swelling Index	Maximize			

Outcomes of independent factors upon dependent variables at three levels were determined using the following non-linear quadratic model expression, where dependent variable is Y, b_0 arithmetic mean, Y_1–Y_{123}

are the regression coefficients of acceptable variables. The factors X_1, X_2, and X_3 show, how the various parameters interact with one another.

$$Y=b_0+Y_1X_1+ Y_2X_2+ Y_3X_3+ Y_1Y_2X_1X_2+Y_1Y_3X_1X_3+Y_2Y_3X_2X_3+ Y\ {}^{2}_{1}X\ {}^{2}_{1}+Y\ {}^{2}_{2}X\ {}^{2}_{2}+Y\ {}^{2}_{3}X\ {}^{2}_{3}$$

Eq:- 1

Wet granulation method for granules'preparation

Wet granulation method was adopted for core tablets' fromulation as per composition given in table 2.

In wet granulation method, all the excipients and active pharmaceutical ingredient were first allowed to pass through sieve no 80 individually. After that all the accurately weighed polymers and excipients were allowed to thoroughly mix in pestle and mortar. Prepared granules were allowed to pass through sieve no. 20. These were made moisture free at 45°C in hot air oven. Magnesium stearate and talc were sprinkled on granules[9].

Characterization of granules

The granules were characterized for their flow-properties, bulk-density, tapped-density, angle of repose along with Hausner's ratio[7].

Preparation of core tablet

The compressiblity and flow properties of granules were recorded. Tablets were punched with average weight of 180 mg and hardness 7 kg/cm^{2}using eight station punching machine to a desired size, shape and thickness [10].

Table 2: Composition of osmotic tablets F1-F15

Drug/ Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Acarbose (mg)	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
NaCl (mg)	30	40	30	40	30	40	30	40	35	35	35	35	35	35	35
MCC (mg)	60	60	60	60	50	50	70	70	50	50	70	70	60	60	60
Magnesium stearate (mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Talc (mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
PVP K30 (% w/w)	2	2	4	4	3	3	3	3	2	4	2	4	3	3	3
Lactose q.s. to 180 mg	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Method for preparing coating-solution and tablets' coating

Cellulose acetate phthalate (CAP) added with polyethylene glycol (PEG) 400 (in ratio 5:1) in acetone and IPA in ratio 1:1 were added to prepare coating solution. Mixture was stirred till the solution get clear. CAP along with PEG 400 were utilized as semipermeable membrane provider and as plasticizer respectively. To coat core tablets with coating solution, conventional coating pan was utilized. Pan speed, coating inlet air, temperature, atomizing air pressure and spray rate, all parameters of coating process i.e. were optimized. Weight gain was checked by periodically checking the average weight of tablets to acquire the desired weight of tablets. The layered tablets were made moisture free at 50°C intended for half an hour in conventional pan coater at 1-2 rpm[11].

Evaluation of formulated tablet

Post-compression parameters

All the coated and uncoated tablets were evaluated for various factors i.e. morphological properties, weight variation, hardness and friability, swelling study, drug content and in vitro dissolution studies[11-15].

Stability studies

Optimized formulation F10 was placed in an airtight container and kept at two different storage conditions as per ICH guidelines (25 °C/60 % RH and 40 °C /75 % RH) for 90 days. After 15, 30, 45, 60, and 90 days, samples were assessed for remaining drug-content. Initial drug content was assumed to be 100%[16].

Results and Discussion

Pre-formulation profiling

Sample drug was identified by profiling several analytical techniques including FTIR spectroscopy, melting point determination and solubility determination. All of the parameters were confirmed, found acceptable as per official compendia specifications. The compatibility studies were also carried out between drug and excipients and data is already mentioned in previous research paper.

Percetange assay of Acarbose (50 mg)

HPLC was employed for doing assay of obtained sample and the sample was identified. Assay of working standard solutions of drug sample containing 50 mg of active pharmaceutical ingredient was carried out. The HPLC reading and graph have been shown in table 3:

Percentage RSD of five replicates of standard solution is 0.41 which is less than 2%. Theoretical plates of each injection are more than 2,000 and tailing factor is less than 2 for each injection. Hence, as per U.S.P. standard solution passes system suitability criteria.

Table 3: Assay of acarbose (50 mg) by HPLC

S. No.	Sample name	Vial	Inj.	Name	RT	Area (AS)	USP Plate count	USP Tailing
1	W standard	2	1	Acarbose	7.076	705502	3501.23	1.59
2	W standard	2	2	Acarbose	7.077	707007	3633.34	1.58
3	W standard	2	3	Acarbose	7.075	700184	3622.18	1.56
4	W standard	2	4	Acarbose	7.076	701075	3680.37	1.56
5	W standard	2	5	Acarbose	7.077	702903	3666.08	1.56
Mean					7.076	703334.349	--	--
Std. Dev					0.001	2889.74	--	--
% RSD					0.01	0.41	--	--

Box behnken statistical optimization of osmotic tablet

For the optimization of osmotic tablets, Box-Behnken design was employed. Along with their binary interactions and polynomial effects, each independent factor was investigated on three different levels. The % cumulative drug release at 16th hrs and % swelling index were examined. Table 4 represents independent variable's influence on dependent variants and regression analysis. Equations 2 and 3 were used to apply quadratic mathematical models to examine interaction among the independent components and investigated outcomes.

Fitting data to model

Independent variables' effect was examined for chosen dependent variables. Best-fitting models for the percentage of drug-release along with swelling index were determined by fitting observed data into an ANOVA. It was noted that the correlation coefficients, which were computed using the experimental values, adequately accounted for the data. Tables 4 and 5 display values of R2, corrected R2, and predicted R2. High value of F and a small value of p (less than 0.005) suggested that dependent variables observes a significant influence due to independent variants.

Table 4:- ANOVA of the fitted equation for the percentage drug release at 16th hour

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	311.47	9	34.61	65.37	0.0001	Significant
A-Nacl	70.09	1	70.09	132.39	< 0.0001	
B-PEG	58.75	1	58.75	110.97	0.0001	

C-MCC	101.82	1	101.82	192.31	< 0.0001	
Residual	2.65	5	0.5294			
Lack of Fit	2.62	3	0.8721	56.51	0.0174	Significant
St. Deviation	0.73					
R^2	0.99					
Adjusted R^2	0.97					
Predicted R^2	0.86					
Model	Quadratic					

$Y_1=81.42+2.96X_1+2.71X_2-3.57X_3+ 0.29X_1X_2-0.33X_1X_3-0.36X_2X_3-0.85X^2_1-1.15X^2_2-4.55X^2_3$

Equation 2

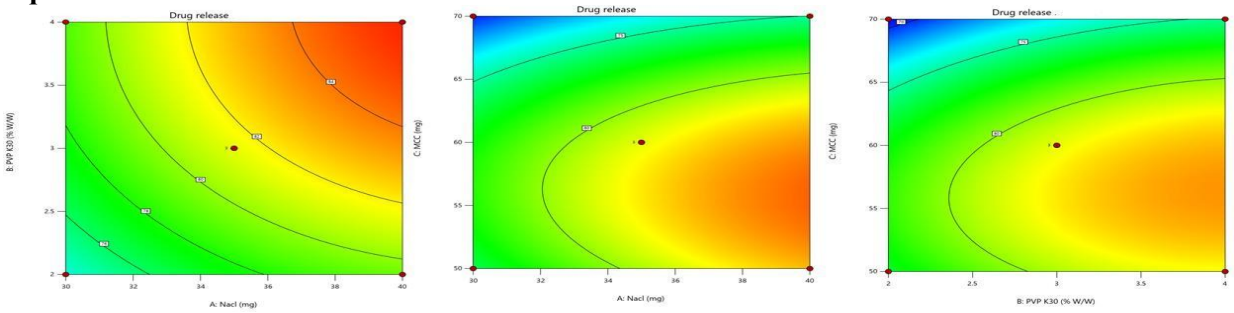

Figure 1: Contour plots displaying influence of independent variables on drug release

The contour plots as well as the 3D surface plot shown in Figure 1 and 2, illustrated that with the increase of the concentration of NaCl and PVPK30, the incresaed % cumulative drug release was also observed. Whereas, amount of MCC negatively affect drug release.

Table 5:- ANOVA of the fitted equation for the swelling index

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	6763.27	9	751.47	42.86	0.0003	significant
A-Nacl	1624.50	1	1624.50	92.65	0.0002	
B-PEG	1458.00	1	1458.00	83.16	0.0003	
C-MCC	1922.00	1	1922.00	109.62	0.0001	
Residual	87.67	5	17.53			
Lack of Fit	2.7	5	34.70	3.95	0.087	significant
St. Deviation	1.9					
R^2	0.98					
Adjusted R^2	0.96					
Predicted R^2	0.82					
Model	Quadratic					

$Y_2=122.3+14.25X_1+13.50X_2-15.50X_3-0.25X_1X_2-4.25X_1X_3+1.25X_2X_3-4.04X^2_1-8.54X^2_2-20.04X^2_3$

Equation 3

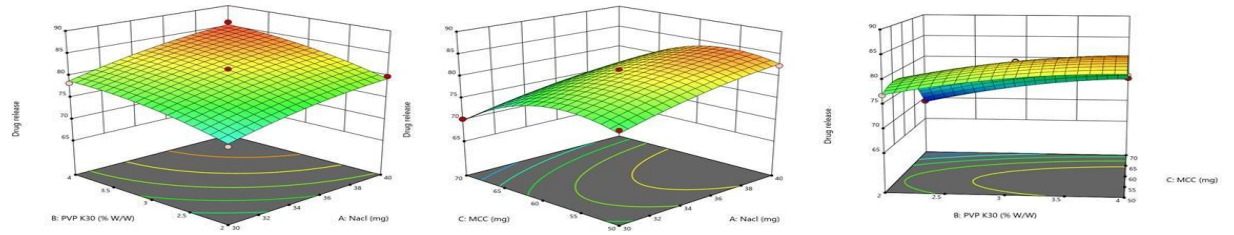

Figure 2: 3D surface plots illustrating the influence of independent variables on drug release

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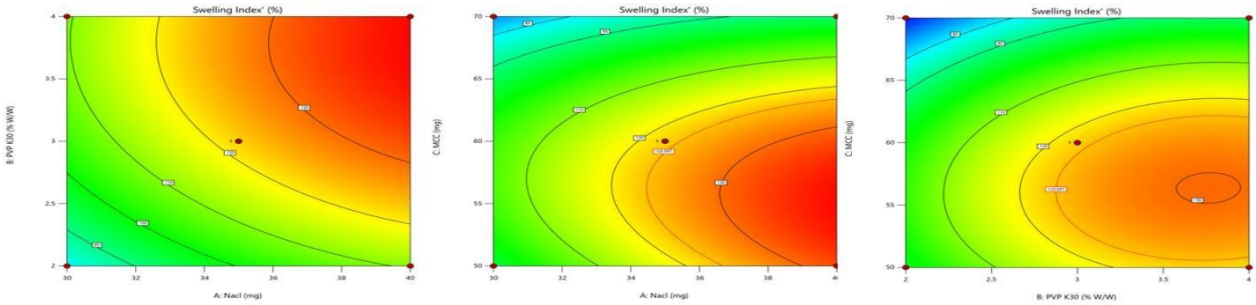

Figure 3: Contour plots depicting the effect of independent variables on % swelling index

As illustrated in figure 3 and 4, as amount of NaCl and PVPK30 increased, the modified % swelling index was observed owing to osmotic effect of NaCl which increase water absorbing capacity of tablets and develop pores in it. Whereas, at the optimum concentration of MCC, the maximum effect was observed.

The formulation F10 having drug release of 75.46% at 16th hrs and % swelling index of 123 % was selected for further studies. This formulation was made with 35 mg NaCl, 4% w/w PVPK30 and 50 mg of MCC.

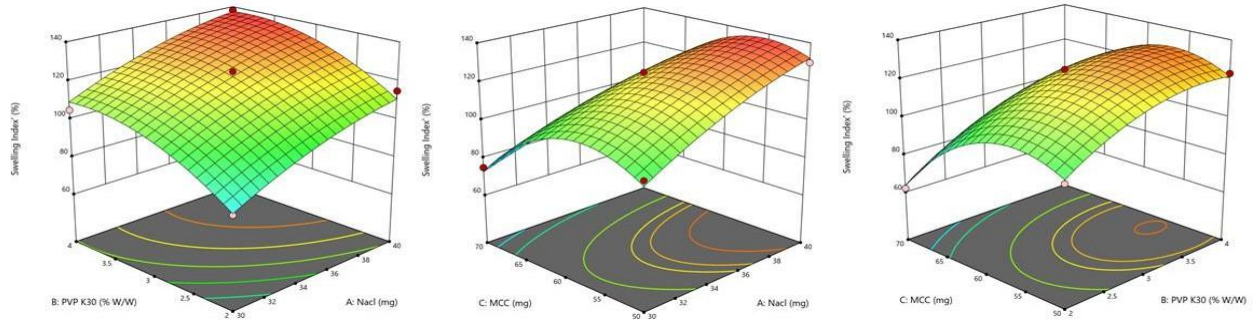

Figure 4: 3D surface plots depicting influence of independent variables on % swelling index

Characterization of osmotic tablets

Pre-Compression parameters

Granules evaluation

The granules of formulations F1–F15 were assessed for various parameters, i.e. bulk density, tapped density, angle of repose and, Hausner's ratio. Bulk density was determined to be within range 0.389±0.51 to 0.587±0.19 gm/ml. The tapped density was determined to be between 0.491±0.09 to 0.715±0.26 gm/ml as shown in figure 5. Hausner's ratio was calculated within ranges of 1.09±0.38 to 1.40±0.18, respectively. The results of Hausner's ratio and angle of repose revealed good flow characteristics of all formulations.

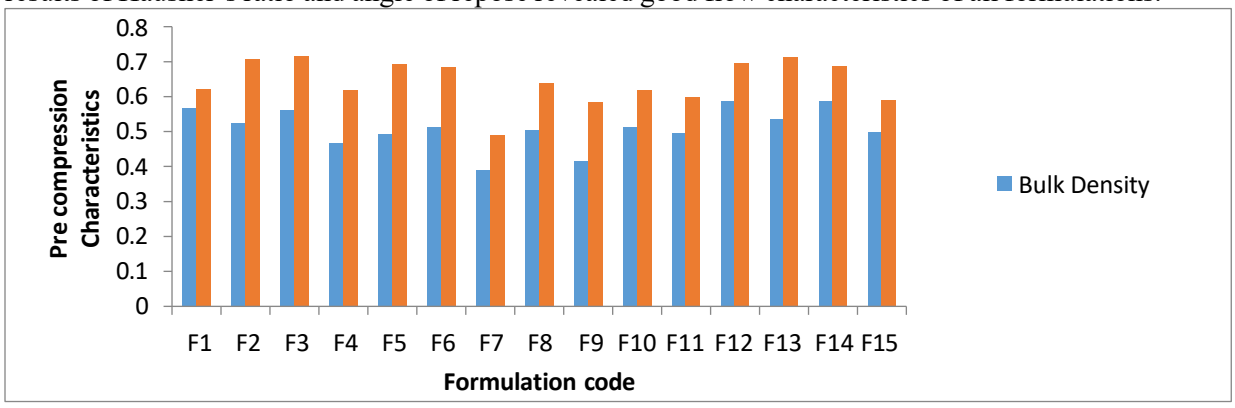

Figure 5: Pre-compression characteristics of granules

Post-Compression parameters for uncoated tablets

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The formulations F1-F15 were evaluated for various parameters. Thickness of all the formulations was found in the range of 4.4±0.36 to 6.0±0.42 mm. Tablets have a hardness range of 5.24±0.76 to 7.04±0.56 kg/cm2. The thickness and hardness of all formualtions before and after compression are shown in figure 6. Average weight of uncoated and coated tablets was observed in specified limits. The percentage friability of osmotic tablets was observed in the range of 0.514±0.21 to 0.789±0.51%. Friability refers to the tendency of a tablet to chip, crumble, or break during handling, packaging, and transportation.

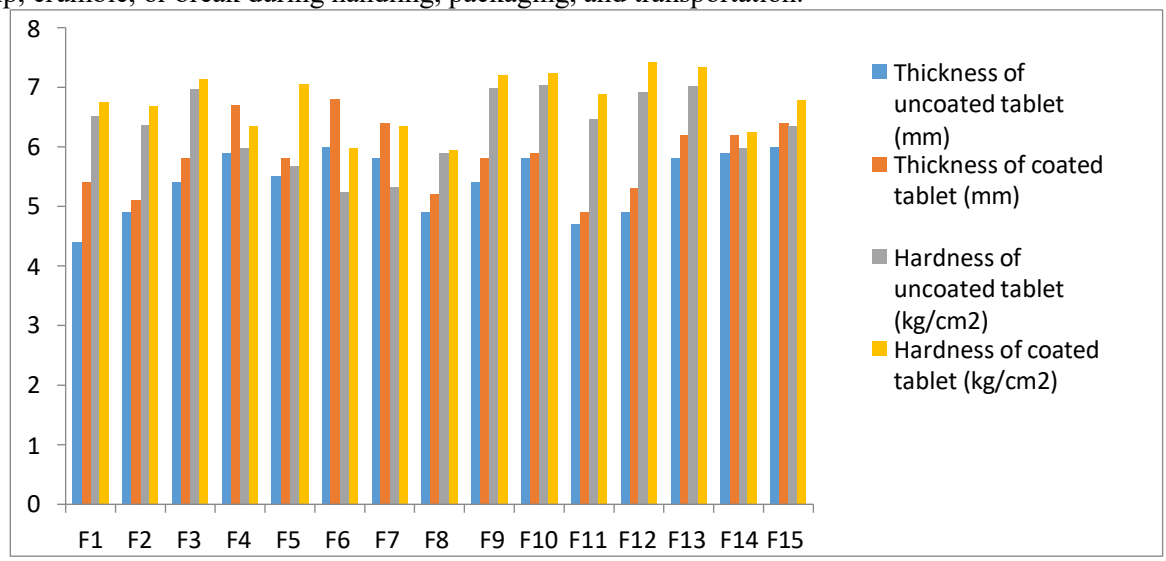

Figure 6: Comparison of Pre and Post comparison of thickness and hardness of different formulations

Post-Compression parameters for coated tablets

All formulations were found to be soft, smooth without any imperfections. The thickness of all formulations was found within range of 5.1±0.34 to 7.85±0.37 mm as mentioned in figure 6. Tablets have a hardness range of 5.12±0.27 to 7.65±0.03 kg/cm2 as mentioned in figure 6, pre and post compression. Swelling studies of osmotic tablets were carried out and were found to be in the range of 62±0.18 to 138±0.26%. Average weight of uncoated and coated tablets is illustarted in figure 7 and was found to be in specified limits. Drug-content of all formulations was observed as almost uniform and was found in a range 98.89 to 101.83 %, possessing good drug-content uniformity. Results of drug-content and % swelling index is mentioned in figure 8.

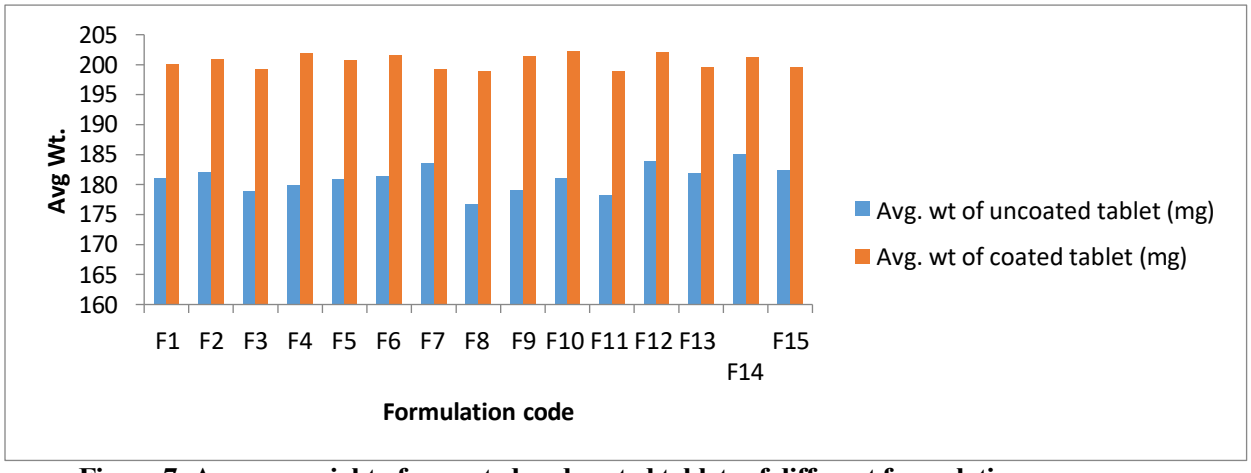

Figure 7: Average weight of uncoated and coated tablets of different formulations

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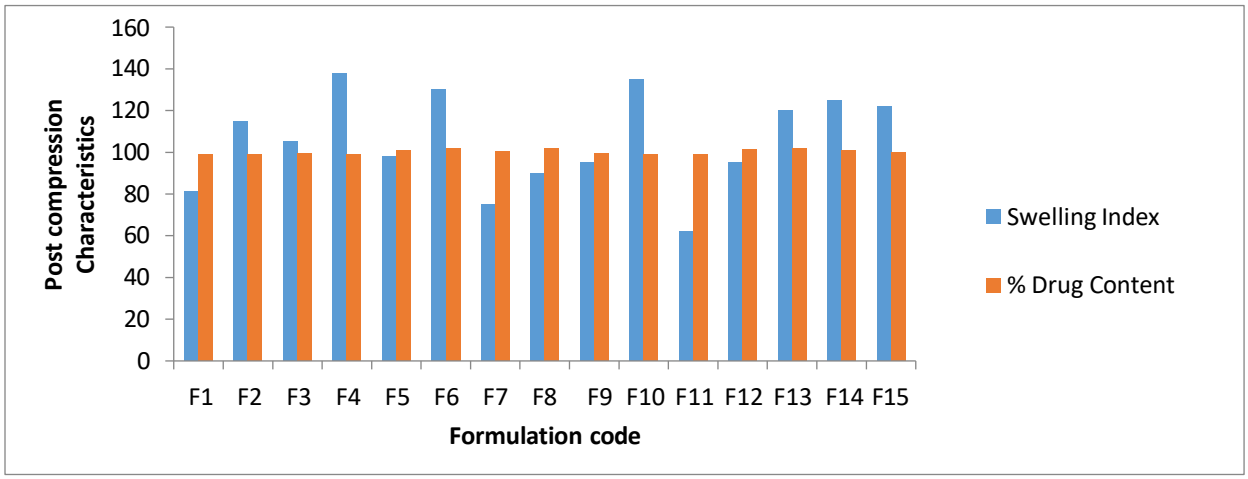

Figure 8:Comparative evaluation of % swelling index and % drug content of coated tablets

In vitro percentage release study of osmotic tablets

The results of all the fifteen formulations have been mentioned in figure 9. From the dissolution data it has been observed that F10 formulation released drug at a controlled manner and after 16 h and 24 h found to release 75.46 and 100.52 percent respectively. In vitro drug release studies of various osmotic tablets were performed in different simulated media and its results have been displayed in **figure 9.**

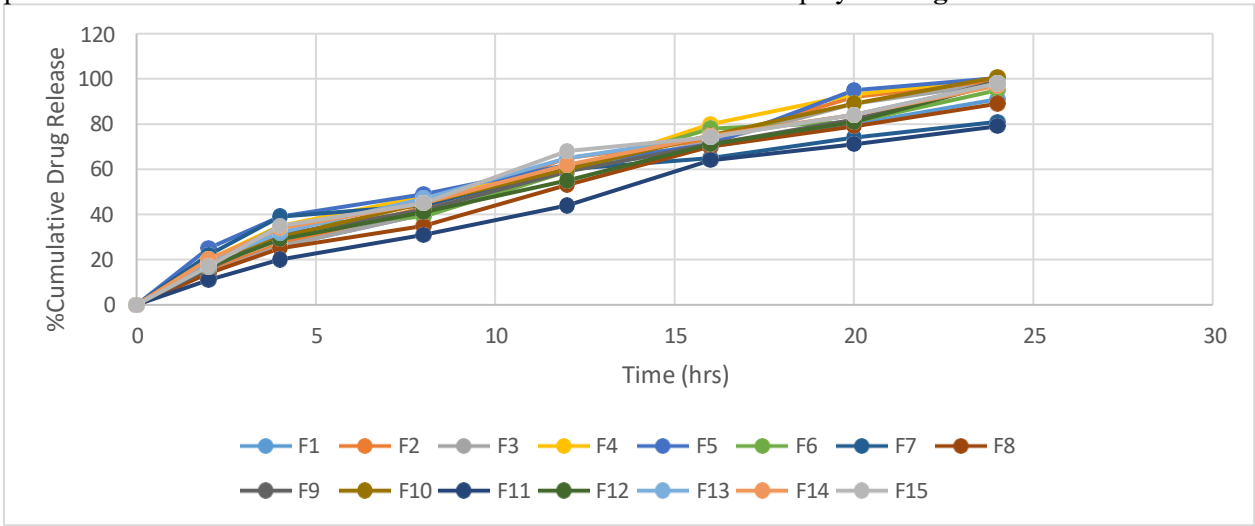

Figure 9: Graph showing percentage drug release from formulations F1-F15

Stability studies

Stability studies of optimized formulation F10 was performed at all previously mentioned storage conditions and it showed good stability for a time period of 90 days.

CONCLUSION

Acarbose-loaded osmotic tablets using a Box-Behnken design with three independent variables: NaCl concentration, PVP K30 concentration, and microcrystalline cellulose concentration were successfully prepared and optimized. This quality by design assisted statistical approach enabled the identification of optimized concentration of different independent variables leading to the development of a controlled release system. The optimized formulation, F10 exhibited the desirable release of drug at controlled rate characteristics across period of 24 hours. This controlled release profile can potentially improve the patient compliance by decreasing the dose frequency and glycemic control in diabetic patients by maintaining therapeutic drug levels over an extended period of time. Swelling index of F10 was also observed to be

optimal, indicating a suitable balance between drug release and tablet integrity. This balance is crucial for ensuring consistent drug delivery and preventing dose dumping. Results revealed that the Box-Behnken design is a valuable means for optimizing osmotic tablet formulations, allowing for the identification of key factors influencing drug release and swelling index. Further studies are warranted to evaluate experiments in animals as well as clinical implications of this optimized formulation, including bioavailability and bioequivalence studies, as well as clinical trials to assess its efficacy and safety in diabetic patients.

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