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Quality by Design (QbD) Based Formulation and Characterization of Acarbose's Osmotic Controlled Release Tablets

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ABSTRACT

Acarbose, an oral hypoglycemic drug belonging to II class BCS was selected as a model drug for preparation of controlled porosity osmotic drug delivery system. Active pharmaceutical ingredient was identified for its purity by melting point determination, FTIR and assay by HPLC method. Granules were formulated by wet granulation method after addition of all excipients with drug. The granules were characterized for preformulation studies such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Formulations were designed and optimized by 3^2 full factorial design using Stat-Ease 360 software. The effect of two independent variables i.e. concentration of mannitol (X_1) and concentration of microcrystalline cellulose (X_2) was evaluated on percentage cumulative drug release at 8 hrs and hardness of tablets. The prepared formulations were evaluated in terms of hardness, friability, drug content, weight variation and percentage cumulative drug release and the optimized formulation was characterized for stability studies. The results of optimized formulation F3 states that as the concentration of mannitol and microcrystalline cellulose increased, the percentage drug release and hardness were also found to increase.

Keywords: *Characterization, formulation, osmosis, DoE, osmotic agents, acarbose, optimization.*

1. INTRODUCTION

An alteration in the metabolism of lipids, carbohydrates as well as proteins is known as hyperglycemia and all are characteristics of syndrome known as diabetes mellitus. Type 2 diabetes is a heterogenous disease characterized by number of defects in pancreatic β cells, liver along with peripheral tissues such as skeletal tissues and adipose tissues. Increase in glucose level takes place due to absolute or relative insulin shortage. Long term effect of hyperglycemia causes ocular, renal, cardiovascular and neurological problems [1].

Acarbose is an intestinal alpha glucosidase inhibitor and possess inhibition against sucrose and utilized in therapy of diabetes mellitus type II. The normal dose of acarbose is 25 mg for the treatment of hyperglycemia exceeding to 100 mg three times a day and available in market as 25, 50 and 100 mg tablets. They possess much reduced systemic bio availability due to which shows less side effects compared to contemporary anti-diabetic drugs. Biological half-life of acarbose is 2 h [2].

Oral route offers maximum surface area for absorption among all drug delivery system for administration of various drugs that's why it is the most preferred and convenient choice. Conventional dosage form suffers from various disadvantages such as fluctuation in plasma concentration, multiple dosing, poor bio-availability, first pass metabolism leads to patient in-compliance. Release of drug from novel drug delivery systems offers controlled release of drug at target site for better

therapeutic action. Compared to conventional therapies, novel drug delivery system provides predictable plasma concentration, target the drug to the target site, thereby, reducing the dose, frequency of dosing, toxic side effects and fluctuation in plasma level ultimately leads to patient compliance and reduced drug accumulation [3-5]. Now a days, various novel drug delivery systems are under investigation by number of researchers. Osmotically controlled oral delivery system is one such novel dosage form and proved as one of the most promsing novel approach for oral delivery of drug in recent time. Osmosis is the triggering factor that is responsible for controlling the drug release from the polymer matrix and osmotically controlled devices. This system provides release of drug at uniform rate and enhanced concentration at the site of absorption. Release of the drug from this system is not dependent upon pH along with other physiological factors to a great extent. By optimizing the properties of drug and this delivery system, it is possible to modify the release characteristics [6-10].

Controlled porosity osmotic drug delivery system is a spray coated tablet containing semipermeable membrane along with dis-solvable pore forming agents without any aperture to release the drug. Release of the drug takes place through the pores formed in the semipermeable wall in situ. Release of the drug from osmotic tablet occurs after its dissolution inside the core by hydrostatic force and diffusion through the pores created by dissolution of pore formers incorporated in the membrane [11].

The aim of the present work is to emphasize the need of controlled release formulation of acarbose for better control of blood glucose level, to lessen gastrointestinal disturbance, to prolong its therapeutic effect and to improve patient compliance as well as clinical efficacy.

2. MATERIALS AND METHODS

Acarbose was obtained as gift sample from Innova captab, Baddi, Himachal Pradesh, India. Cellulose acetate phthalate was purchased from Yarrow Chem Product, Mumbai, India. Mannitol, magnesium stearate, isopropyl alcohol and talc were purchased from S D Fine Chem Limited, Mumbai, India. Microcrystalline cellulose, PEG 4000 and PVP K30 were purchased from Loba Chemie, Mumbai, India. All the chemicals used were of analytical grade.

Methodology

Pre-formulation Studies

Identification of pure drug (acarbose)

The pure drug sample of acarbose was identified by FTIR and melting point determination and compared with reference of drug as provided in Indian Pharmacopoeia and literature.

Solubility determination

The solubility of drug sample was determined spectrophotometrically in different solvents [12].

Determination of drug-polymer interaction by FTIR

The IR spectrum was taken of the obtained sample of drug and the combination of excipients and drug sample. The spectrum of obtained drug sample was compared with the standard spectra to confirm the purity of acquired sample of drug and compatibility with the excipients.

Percentage assay of acarbose by HPLC

The obtained sample of drug was identified by doing assay of acquired sample using HPLC. Assay of working standard solutions of drug sample was carried out.

Experimental design for acarbose osmotic controlled release tablets

Nine formulations of osmotic tablet using using 3^2 full factorial designwere developed. Table **1** shows the selection of two independent variables: concentration of mannitol (X_1) and concentration of MCC (X_2). With respect to these two independent variables, two dependent variables were chosen which were hardness (Y_1) and percentage drug release (Y_2).

Table 1: Test Factors for optimization of process parameters

Factor	Name	Units	Low Level	Middle Level	High Level
A (X_1)	Conc. of mannitol	mg	15	25	35
B (X_2)	Conc. of MCC	mg	15	25	35

Preparation of granules by wet granulation method

All the excipients and drug mentioned in table 2 excluding talc and magnesium stearate were mixed with isopropyl alcohol with stirring. The dried blend was converted into granules using binder solution. The dough mass was passed through sieve to prepare granules and dried in hot air oven at 50°C. Dry granules were passed through sieve no. 20 to obtain uniform sized granules. Magnesium stearate and talc were sprinkled on the granules to overcome the force of friction between walls of die and punch and intermolecular adhesion [13].

Characterization of Granules

Pre-compression Parameters

The granules of formulations F1-F9 were evaluated on the basis of various pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio as well as angle of repose [14].

Angle of repose

The prepared granules containing drug and excipients were evaluated for their flow ability using angle of repose by funnel method.

Bulk density

Bulk density of prepared granules was calculated by placing its weighed quantity in graduated tube and volume was determined. Bulk density was calculated by the following given formula:

$$\text{Bulk density (gm/ml)} = \frac{\text{Weight of samples in gms}}{\text{Volume acquired by the sample}}$$

Tapped density

Tapped density of granules was calculated by same density apparatus by which bulk density was calculated. In this method, granules were poured smoothly through the wall of cone in graduated cylinder of 100 ml. Graduated tube was fixed in the instrument and parameters were set to perform the test [15]. Volume occupied by granules after appropriate number of taps was recorded and calculated by the following formula:

$$\text{Tapped density (gm/ml)} = \frac{\text{Weight of samples in gms}}{\text{Volume acquired by the sample}}$$

Hausner's ratio

It provides the extent of densification that results from vibration of feed hopper. The value of Hausner's ratio close to 1.25 indicates good flow ability, at the same time as greater than 1.5 indicates poor flow characteristics [16,17].

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Preparation of core tablet

After the characterization of granules such as testing its compressiblity and flow properties, granules were then mixed with magnesium stearate and talc was sprinkled on it. The tablets were punched with average weight of 125 mg and hardness 7 kg/cm^{2}employing eight station punching machine to a desired size, shape and thickness [18].

Table No. 2: Composition of osmotic formulations F1-F9

Drug/Excipients	**Formulations**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Acarbose (in mg)	25	25	25	25	25	25	25	25	25

Mannitol	25	15	25	15	15	35	25	35	35
Microcrystalline cellulose	25	35	15	15	25	25	35	15	35
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
PVP K30	10	10	10	10	10	10	10	10	10
Lactose Q.S to 125 mg	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Preparation of coating solution

Coating solution was prepared by adding cellulose acetate phthalate (CAP) and polyethylene glycol (PEG) 400 (in ratio 5:1) in acetone and IPA in ratio 1:1. Mixture was stirred until the formulation of clear solution. CAP was utilized as semipermeable membrane provider and PEG 400 was used as plasticizer.

Coating of tablets

Conventional coating pan was employed to coat the core tablets with prepared coating solution. All the parameters of coating process i.e. pan speed, coating inlet air, temperature, atomizing air pressure and spray rate 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 dried at 50 °C intended for 30 minutes in conventional pan coater at 1-2 rpm.

Post-compression parameters

All the coated and uncoated tablets were evaluated fro various parameters such as morphological properties, weight variation, hardness and friabiltiy [19,20].

Morphological Properties

Morphological characteristics of osmotic tablet such as homogeneity, color and appearance were examined visually.

Average weight of coated and uncoated tablet

Twenty tablets (n = 20) from each batch were weighed using electronic balance and their average weight was calculated.

Friability

Twenty tablets (n = 20) of each batch were weighed and put into the friabilator drum. After 100 revolutions of friabilator, tablets were recovered. The tablets were then freed from dust and weighed. Friability was calculated from the following given equation [21]:

$$\%\ \text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Hardness

Twenty tablets (n = 20) were taken for the hardness test using a hardness tester. The tablet was placed between the two probes, of which, one is a movable probe and another is an immovable probe of the hardness tester. Then the force was applied from the movable probe. The force to break the tablet was recorded, which was taken as the hardness of the tablet [22].

Swelling study

The osmotic tablets of acarbose were weighed individually (W_1) and placed separately in a glass beaker containing 200 mL of phosphate buffer of pH 6.8 incubated at 37 ± 0.5 °C. At regular 1 h time intervals until 10 h, the tablets were removed from beaker and the excess surface liquid was removed carefully using the paper. The swollen tablets were then re-weighed (W_2) and the swelling index (SI) was calculated using the following formula [23]:

$SI = (W_2 - W_1)/W_1$

Drug content

The tablets from each batch were taken in a volumetric flask of 10 ml containing phosphate buffer buffer of pH 6.8. The

resulted mixture was then shaken on a mechanical shaker till a homogenous solution was prepared and filtered. The absorbance was measured using UV visible spectrophotometer after proper dilutions and drug content was determined [24].

***In vitro* dissolution studies**

In vitro drug release studies of various formulations were performed using USP II (paddle with sinker) at 100 rpm in 900 mL of phosphate buffer of pH 6.8 which was maintained at 37 ± 0.5 °C. Then 1 mL of sample was withdrawn at predetermined time intervals until 24 h and replaced with fresh dissolution medium. The samples were analyzed by UV visible spectrophotometer at 210 nm [25].

Stability studies

The optimized formulation F3 was placed in an airtight container and kept at two different storage conditions as mentioned in 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 the remaining drug content. The initial drug content was assumed to be 100% [26,27].

3. RESULTS & DISCUSSION

Preformulation characteristics

Identification of pure drug (acarbose)

The pure drug sample of acarbose was identified by FTIR and melting point determination. The drug sample was compared with reference of drug as provided in Indian Pharmacopoeia and literature. The melting point of obtained sample of acarbose, an antidiabetic drug was checked by melting point apparatus and was found to be 164-166 °C which was comparable to its reported value i.e. 165-170 °C.

The drug acarbose exhibits, peak at 3450 cm^{-1} due to hydroxyl stretching, 1643 cm^{-1}, due to C=C stretching, 1045 cm^{-1} due to C-O stretching and hydroxyl bending vibrations at 1452 $cm^{-1.}$. The peaks at 1081 cm^{-1} and 1045 cm^{-1} confirms about the peaks of acteyl group. The drug showed no interaction with the excipients as the selected excipients were inactive in nature.

From the melting point determination and FTIR, it was concluded that obtained sample of drug was pure.

Solubility determination

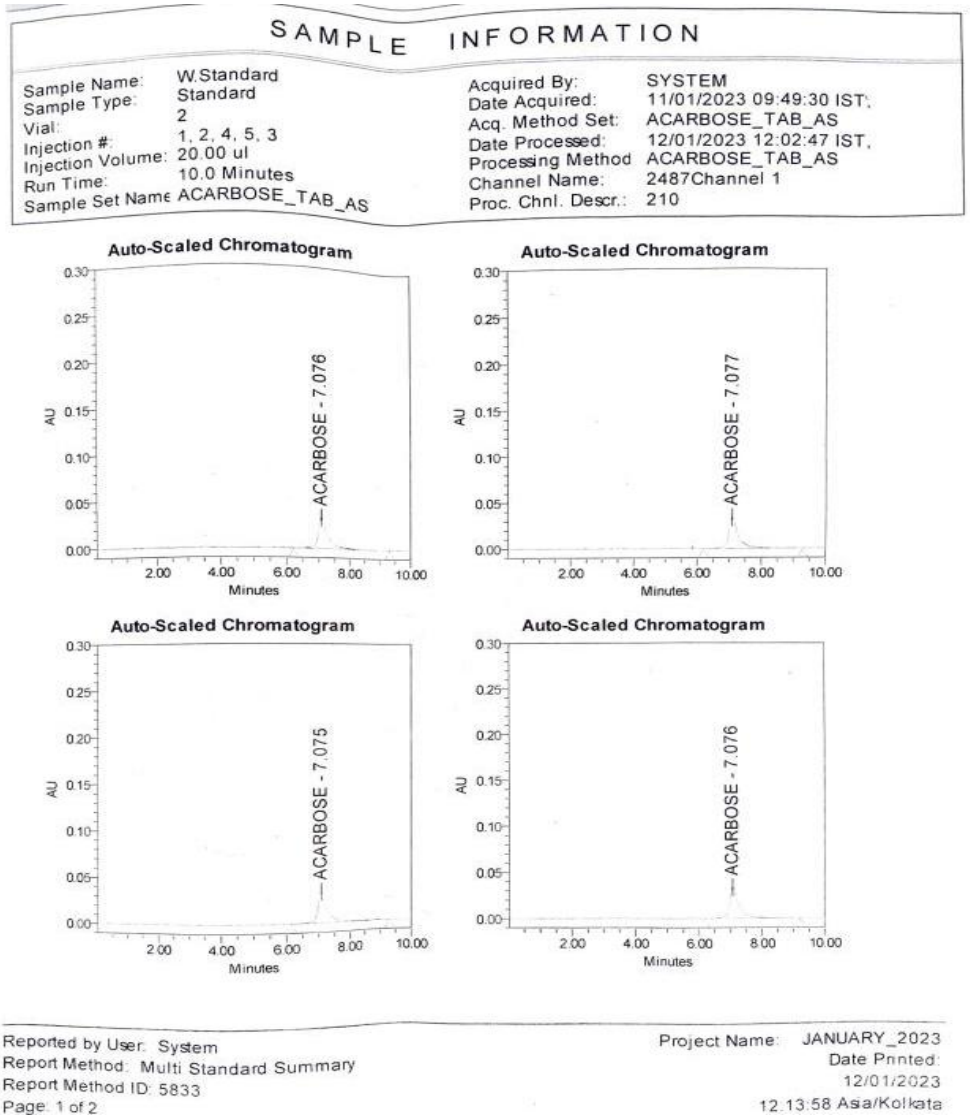
The solubility of drug sample was determined spectrophotometrically in various solvents. It was found to be very much soluble in water, soluble in methanol and practically insoluble in dichloromethane.

Percentage assay of acarbose (25 mg)

The obtained sample of drug was identified by doing assay of acquired sample using HPLC. Assay of working standard solutions of sample containing 25 mg of active pharmaceutical ingredient was carried out. The HPLC reading and graph have been shown in table 3and figure 1:

Table 3: Assay of acarbose (25mg) by HPLC

S. No.	Sample name	Vial	Inj.	Name	RT	Area (AS)	USP Plate count	USP Tailing
1	W standard	2	1	Acarbose	7076	720507	3487.51	1.65
2	W standard	2	2	Acarbose	7077	724503	3616.74	1.64
3	W standard	2	3	Acarbose	7075	722783	3599.27	1.64
4	W standard	2	4	Acarbose	7076	719131	3663.36	1.61
5	W standard	2	5	Acarbose	7077	720014	3649.81	1.60
Mean					7076	721387.811	3603.34	1.63
Std. Dev					0.001		69.60	0.02
% RSD					0.01		1.93	1.30



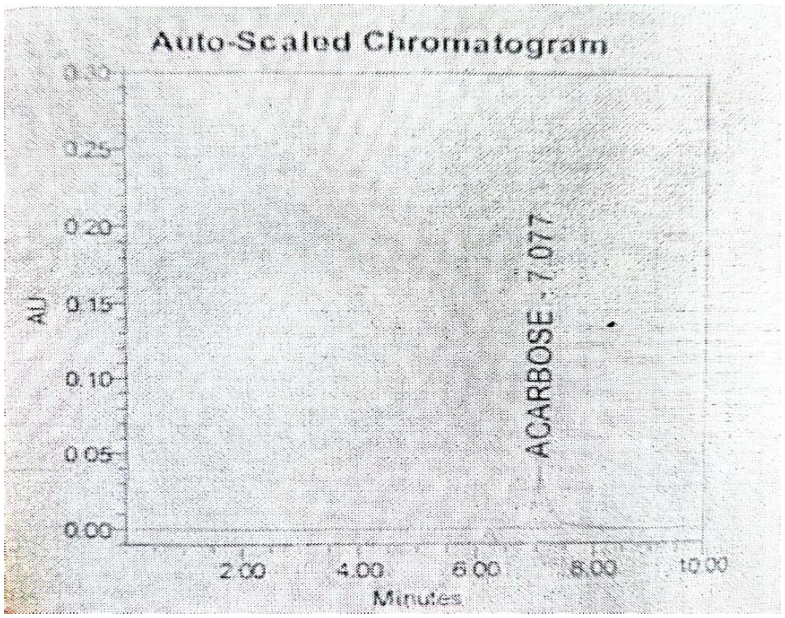


Figure 1: Chromatogram of acarbose

Determination of drug-polymer interaction by FTIR: As the excipients were inactive so no FTIR was done of excipients and drugs.

Optimization of various parameters by Full Factorial Design

The results obtained after implementing 3^2 Full Factorial design have been mentioned below.

The regression equation for cumulative particle size obtained after calculation of main and interaction effects is represented in given equation (a) and the corresponding 3D surface graph.

Analysis Summary

The analysis summary is presented in table 4 and p value of both the response was less than 0.001 which states that model is highly significant. Contour plot and 3 D surface plot indicating the effect of independent variable on percentage cumulative release have been shown in figure 2.

Table 4: Analysis summary of percentage cumulative drug release and hardness

Variable	P value	Std. Deviation	C.V.%	Adequate R^2	Predicted R^2
Drug release	0.0004	0.47	0.62	0.99	0.97
Hardness	0.0019	0.103	2.90	0.99	0.97

$Y_1=76.21+2.60X_1+6.15X_2+0.30X_1X_2-0.64X_1^2+0.75X_2^2$…….(a)

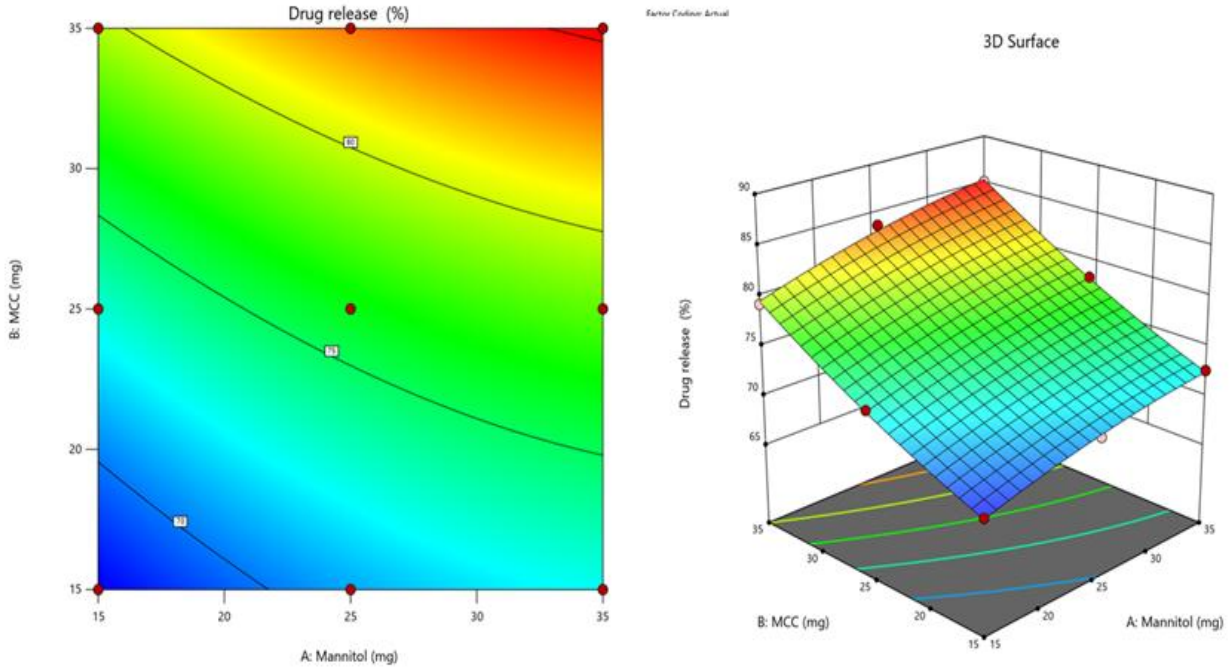


Figure 2: Contour plot and 3D surface plot showing the effect of independent variable on percentage cumulative drug release

From the equation and figure, it was observed that as the concentration of mannitol and MCC increased the percentage cumulative drug release was also found to be increased, hence, both the variables were found to positively affect the drug release.

Y2: Hardness

The regression equation for entrapment efficiency obtained after calculation of main and interaction effects is represented in given equation(b) and the corresponding 3D surface response graph is shown in **figure 3.**

$Y_1=3.73+0.31X_1+0.83X_2-0.015X_1X_2-0.106X_1^2-0.116X_2^2$……(b)

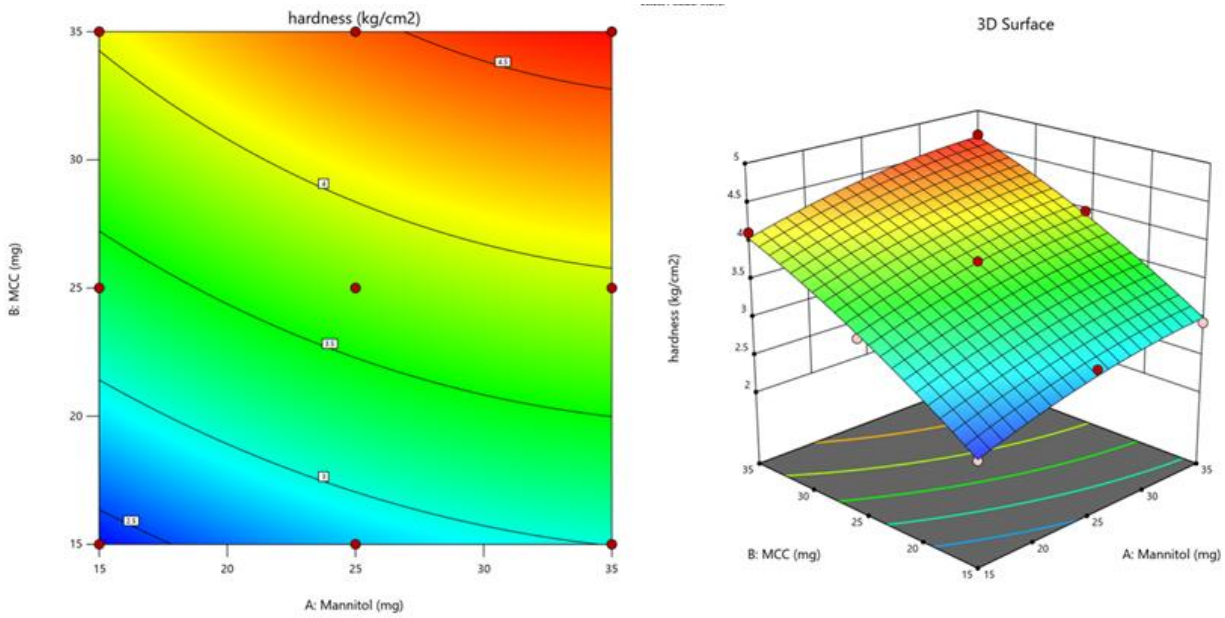


Figure 3: Contour plot and 3D surface plot showing the effect of independent variables on hardness

From the equation and graph, it was observed that as the concentration of mannitol and MCC was increased the hardness was also found to be increased, hence, both the variables positively affected the hardness of osmotic tablets.

Characterization of Tablets

Pre-compression parameters

Granules evaluation

The granules of formulations F1-F9 were evaluated for various parameters such as bulk density, tapped density, Carr's index, Hausner's ratio as well as angle of repose. The data of all these parameters is given in table 5. The bulk density was found to be in range 0.399-0.552 gm/ml. The tapped density was found to be in range of 0.537-0.678 gm/ml. The carr's index and Hausner's ratio was found to be in the limit 16.5-27.3% and 1.20-1.38 respectively. Angle of repose of all formulations were found to be in range of 30.2-39.5°. All the granules of formulations F1, F2, F3, F5 and F6 exhibited good flow properties and were subjected to pass the process of compression into tablets.

Table 5: Preformulation characterization of formulations

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose
F1	0.487±0.14	0.622±0.24	21.7±0.13	1.28±0.03	31.9±0.29
F2	0.489±0.25	0.606±0.21	19.3±0.11	1.24±0.05	30.3±0.11
F3	0.552±0.11	0.661±0.22	16.5±0.20	1.20±0.02	30.6±0.26
F4	0.517±0.28	0.642±0.19	19.5±0.29	1.24±0.08	34.7±0.23
F5	0.492±0.33	0.678±0.11	27.3±0.28	1.38±0.04	31.4±0.16
F6	0.478±0.21	0.623±0.14	23.4±0.32	1.30±0.11	30.2±0.18
F7	0.399±0.16	0.537±0.19	25.7±0.39	1.35±0.09	39.5±0.21
F8	0.486±0.18	0.618±0.09	21.4±0.28	1.27±0.12	37.2±0.29
F9	0.436±0.25	0.604±0.21	20.0±0.17	1.25±0.07	37.6±0.33

All the values were mean ± S.D. (n=3).

Post-compression parameters

Morphological Properties

All tablets of formulations F1-F9 were found to be soft, smooth without any imperfections.

Drug content

The drug content of all the tablets was found to be almost uniform and was found in a range 99.15 to 100.67 %, and exhibited a good content uniformity as mentioned in table 6.

Average Weight

The average weight of uncoated and coated tablets has been mentioned in table 6 and was found to be in desired range.Average weight of uncoated and coated tablets were found in the range of 124.49±0.27-127.39±0.85 mg and 142.12±0.61-147.89±0.23 mg respectively.

Hardness

Tablets have a hardness range of 5.15-6.93 kg/cm². This hardness ensures adequate mechanical strength for handling and storage while also being soft enough to adhere to the mucosal surface. The results are mentioned in table 7.

Table 6: Evaluation parameters of osmotic controlled release formulations

Formulation Code	% Drug content	Weight of uncoated tablet (mg)	Weight of coated tablet (mg)
F1	99.56 ± 0.18	125.24±0.45	145.13±0.34
F2	99.14 ± 0.19	127.16±1.15	142.12±0.61
F3	99.23± 0.34	123.09±0.76	147.89±0.23
F4	100.13± 0.14	125.89±0.29	147.26±0.17
F5	99.34 ± 0.76	123.23±0.96	145.25±0.18
F6	99.87 ± 0.28	127.39±0.85	146.47±0.26
F7	99.59 ± 0.41	126.46±0.74	145.94±0.83
F8	100.67 ± 0.23	125.36±0.94	144.28±0.89
F9	99.31 ± 0.65	124.49±0.27	143.06±0.19

All the values were mean ± S.D. (n=3).

Friability

The percentage friability of osmotic tablets was found on the range of 0.576 to 0.764%. Friability refers to the tendency of a tablet to chip, crumble, or break during handling, packaging, and transportation. The results are mentioned in table 7.

Table 7: Evaluation parameters of formulations (F1-F9)

Formulation Code	Hardness (kg/cm^2)	Friability (%)	Swelling Studies at 8 h (%)
F1	5.75±0.25	0.576	292±0.45
F2	5.15±0.27	0.672	145±0.09
F3	6.87±0.73	0.587	246±0.86
F4	6.34±0.82	0.593	145±0.76
F5	6.93±0.64	0.654	236±0.08
F6	5.98±0.41	0.764	346±1.87
F7	6.35±0.82	0.752	313±0.98

F8	5.94±0.93	0.590	298±0.67
F9	5.66±0.47	0.679	197±1.45

All the values were mean ± S.D. (n=3).

Swelling Study

Swelling studies of osmotic tablets are crucial for understanding their performance, ensuring proper drug release. These studies assess how much the tablet swells when exposed to a fluid, which is essential for effective drug delivery. All the results are mentioned in table 7.

***In-vitro* dissolution studies**

The results of all the nine formulations are mentioned in table 8 and figure 4. From the dissolution data it has been observed that F3 formulation was found to release the drug at a controlled rate and after 8 h and 24 h found to release 70.55 % and 97.36 percent respectively.

Table 8: *In-vitro* dissolution profile of nine formulations

Time (h)	0	2	4	8	16	24
F1	0	18.08	38.09	55.92	69.27	75.38
F2	0	20.01	42.03	79.27	87.47	95.93
F3	0	15.56	33.75	70.55	82.97	97.36
F4	0	14.43	30.75	67.98	85.29	86.19
F5	0	17.32	35.12	73.15	82.37	88.53
F6	0	20.45	44.48	67.26	76.29	88.28
F7	0	23.78	54.18	83.67	93.76	94.28
F8	0	17.32	39.21	57.61	79.37	81.46
F9	0	26.67	58.12	85.12	92.46	93.38

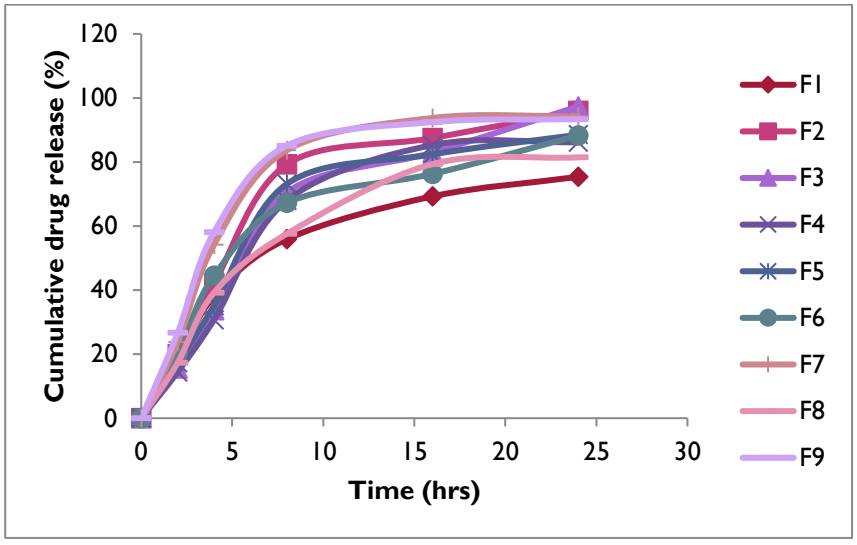


Figure 4: *In-vitro* dissolution profile of formulations (F1-F9)

Stability studies

The stability studies of optimized formulation F3 was carried out at all previously mentioned storage conditions and showed good stability for a time period of 90 days.

4. CONCLUSION

The present study states the successful development and optimization of acarbose containing osmotic tablets using a 3^2 full factorial design, which demonstrated the utilization of quality by design approach formulation development. The optimized formulation (F3) demonstrated improved and controlled drug release characteristics (97±0.36% at 24 h), achieving a good controlled release profile which can mitigate the challenges associated with conventional acarbose formulations. The results suggest that the developed osmotic tablet formulation can enhance the therapeutic efficacy of acarbose by providing a controlled release profile, thereby, improving glycemic control in diabetic patients.

The controlled release profile achieved through osmotic technology may reduce the frequency of dosing, thereby, improving patient convenience and adherence to treatment. Moreover, the stability and reproducibility of the optimized formulation were assured by a thorough assessment of different parameters, such as tablet hardness, friability, and content uniformity.

Further studies are warranted to explore the *in vivo* performance and clinical implications of the 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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