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DEVELOPMENT OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM OF METFORMIN HYDROCHLORIDE

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Keywords:

Metformin hydrochloride, Osmotically controlled drug delivery system (O-CDDS), Polyethylene glycol - 400, dibutyl sebacate, Zero-order release, pH-independent

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ABSTRACT: The aim of the present study was to formulate an osmotically controlled drug delivery system (O-CDDS) of Metformin hydrochloride to reduce the frequency of multiple dosing in non-insulin dependent diabetes mellitus-II which is a lifelong disease. Metformin hydrochloride a BCS Class-III drug having a poor biological half-life of 6 h. O-CDDS of Metformin hydrochloride is a recent approach for the zero-order release profile. Different factors X1 (effect of percentage of plasticizer), X2 (effect of percentage of release modifier), X3 (effect of percentage of coating) were optimized using central composite design. The granules were prepared by wet granulation technique using PVP K90 as a binding agent. Evaluations of granules like bulk density, tapped density, Hausner's ratio, carr's compressibility index, angle of repose was done. Then core tablets were prepared using 16 station tablet press and evaluated for hardness, friability, weight variation. For the preparation of a semi-permeable membrane, the coating of cellulose acetate using polyethylene glycol 400 as a plasticizer was done. Then drilling was done mechanically to create the delivery orifice. Finally, the dissolution was performed and formulation (F-4) was found the best which delivered the drug at zero order. The dissolution data of F-4 was compared with the marketed formulation. This study demonstrated the zero-order release which is independent of pH and hydrodynamics of dissolution.

INTRODUCTION: Diabetes is a lifelong disease and more than 60 million peoples in India are affected by diabetes mellitus (DM)-II nowadays according to the current status. For the treatment of lifelong diseases like diabetes, rheumatoid arthritis, hypertension, *etc*. there is a need for controlled release formulation in which oral route is mostly preferred. Oral drug delivery is the most preferred and convenient route for the administration of therapeutic agents or drugs for systemic action.

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This route is preferred over other routes because it provides improved therapeutic advantages, such as ease of administration, patient compliance, cost-effectiveness and flexibility in formulations. Osmotic pumps are the most promising systems for controlled drug delivery. These systems are used for both oral administration and implantation. The elementary osmotic pump is developed for the present study.

Metformin Hydrochloride is an antidiabetic drug of BCS Class-III which is having high solubility. It belongs to the biguanide class of ant diabetics [1, 3]. It is on the World Health Organization's List of essential medicines, the most effective and safe medicines needed in a health system. Chemically it is 1, 1-Dimethyl biguanide hydrochloride. The biological half-life of the drug is approx 6 h, so

there is a need for the preparation of extended-release dosage form of the drug to reduce the frequency of dosing. There are many approaches for controlling the release like gastro-retentive tablets, floating tablets *etc.* Out of these O-CDDS is a recent approach for the formulation of an extended-release dosage form which can provide a zero-order release profile independent of pH and hydrodynamics of dissolution [4].

In the present study core tablets of Metformin Hydrochloride were prepared using PVP K90 as a binder by wet granulation and then these tablets were coated with cellulose acetate 398-10 using PEG-400 as a plasticizer in different ratios for the optimization using central composite design.

The central composite design was applied using JMP software for the optimization of the factors X1, X2, X3 shown in table I with respect to responses Y1(response of dissolution of 2 h), Y2 (response of dissolution of 6 h), Y3 (response of dissolution of 12 h). The *in-vitro* dissolution data of marketed tablets and optimized batch tablets were compared and it was observed that the optimized O-CDDS batch (F-4) followed zero-order release kinetics while the marketed tablets cannot do this.

MATERIALS AND METHODS:

Materials: Metformin hydrochloride was provided as a gift sample by Sun Pharmaceutical Industries Limited, gurugram; cellulose acetate was supplied by Eastman chemicals; PEG-400 was supplied by clariant products; HPMC K_4M CR was supplied by dow chemical company. Distilled water, analytical grade solvents and reagents used in the whole study.

Methods:

Application of Screening Design: Screening design is intended to find the few significant factors from a list of many potential ones. Its purpose is to identify significant main effects rather than interaction effects. Screening design without center point was applied for the selection of major factors like effect of NaCl which was used as osmogen (0 or 25 mg/tablet), effect of HPMC K_4M CR (0 or 50 mg/tablet), effect of no. of orifice (1 or 2 orifices), effect of plasticizer type (hydrophilic plasticizer; PEG-400 and hydrophobic plasticizer; DBS), effect of % of water in the coating on the release of the drug.

This design suggested eight formulations. Some factors were eliminated and some were selected for the further, optimization of the formulation by central composite design.

Application of Central Composite Design: On the basis of results of screening design, central composite design was applied for the optimization of factors selected by screening design which are X1 {effect of percentage of plasticizer (10, 15, 20 %)}, X2 {effect of release modifier polymer HPMC K_4M CR}, X3 {effect of coating percentage (3, 4, 5%)}.

TABLE 1: COMPOSITION OF CORE TABLETS AND COATING OF DIFFERENT BATCHES OF CENTRAL COMPOSITE DESIGN

	Composition of core tablets				Composition of coating	
Batch code	API (mg/tab)	PVP-K90 (mg/tab)	HPMC K_4M CR (mg/tab)	Mag. stea. (mg/tab)	% Coating	PEG 400 (% of CA)
F-1	500	50	25	5	4	15
F-2	500	50	0	5	5	10
F-3	500	50	0	5	3	20
F-4	500	50	0	5	5	20
F-5	500	50	50	5	5	10
F-6	500	50	0	5	3	10
F-7	500	50	50	5	3	20
F-8	500	50	50	5	4	15
F-9	500	50	25	5	4	15
F-10	500	50	25	5	4	20
F-11	500	50	25	5	5	15
F-12	500	50	50	5	3	10
F-13	500	50	25	5	4	10
F-14	500	50	50	5	5	20
F-15	500	50	25	5	3	15
F-16	500	50	0	5	4	15

In statistics, central composite design (CCD) is an experimental design, useful in response surface methodology, for building a second-order (quadratic) model for the response variable without needing to use a complete three-level factorial experiment. The composition of different batches of core tablets and coating is shown in **Table 1**.

Formulation and Evaluation of Granules of Metformin Hydrochloride: Because of poor compressibility of the API, wet granulation was performed using PVP K-90 as a binder in a rapid mixer granulator (R. M. G). Then obtained granules were dried in fluidized bed dryer (FB dryer) for an appropriate time (10-15 min) and these dried granules were then passed through the 25 # ASTM sieve to obtain uniform granules.

Evaluations like bulk density, tapped density, angle of repose, Hausner's ratio, carr's compressibility index were performed. Tapped density apparatus was used for the determination of tapped density in the tapping order of 10, 250 and 500 tapping. The angle of repose was evaluated using granuheap apparatus. All other evaluations were carried out mathematically.

Formulation and Evaluation of Core Tablets: Core tablets were compressed by 16 stations tablet compression machine (Cad mach, Ahmadabad, India) using 10.5 mm biconvex punches within the hardness range of 15-20 kg. Evaluations like hardness (Dr. Scheulniger hardness tester), friability (Electro lab friability apparatus) and weight variation were performed.

Coating of the Core Tablets: Coating is one of the important steps in the formulation of osmotic pumps. So the coating should be done very carefully. Core tablets were coated with cellulose acetate by taking a concentration of 2% solid content with different plasticizer ratios in solvents.

The coated tablets were dried to remove the residual solvent. The coating was done using gansons coater at bed temperature of 20-30 °C, pan speed of 15-18 rpm, spray rate of 8-10 gm/ml. The time of drying after the coating was 30-40 min.

Creation of Delivery Orifice: Delivery orifices in each tablet were created using a mechanical drill prior to *in-vitro* dissolution.

The creation of delivery orifice is also an important step by which the release rate is to be decided that which diameter of the orifice is required to give the proper release rate [5].

***In-vitro* Dissolution:** USP-I basket type dissolution apparatus was used for *in-vitro* dissolution. Phosphate buffer of pH 6.8 at 37 °C ± 0.5 °C was used as dissolution media. Speed was kept 100 rpm and the volume of media used was 900 ml.

As soon as the temperature of dissolution media meets the target, the tablets were set into the 10 # mesh basket and dissolution was started. Samples were obtained after 2 h, 4 h, 6 h, 8 h, 10 h, and 12 h. An equivalent volume of fresh media was replaced after the collection of each sample to maintain constant dissolution volume and samples were analyzed by UV spectrophotometer at 233 nm [7, 8].

Comparison of *In-vitro* Dissolution Data with Marketed Tablets: *In-vitro* dissolution data for optimized batch (F-4) of the central composite design was compared with marketed tablets of sustained-release Metformin hydrochloride.

RESULTS AND DISCUSSION:

Application of Screening Design: Applied screening design was used for the selection of major factors that were described earlier. The selection of excipients and ratio was done according to this design. On the basis of *in-vitro* dissolution results as shown in **Table 2** of screening design following factors were studied using central composite design with the following range for optimization of the formulation.

HPMC K4 MCR: - 0-50 mg

Coating % Age: 3-5%

% Age of Plasticizer: 10-20%

Following Parameters were Eliminated:

DBS as plasticizer: Because it made the release very slow which we don't require.

% Water: Because of poor film appearance and very low impact on release.

No. of Orifice: Because as compared to 2 orifice 1 orifice made the release more slow at 2 h.

TABLE 2: DISSOLUTION DATA OF DIFFERENT BATCHES OF SCREENING DESIGN

Batch code	2 h	4 h	6 h	8 h	10 h	12 h
E-1	1.1	3.1	5.7	9.1	12.8	22.5
E-2	14.8	37.1	54.3	70.3	83.3	90.2
E-3	14.7	33.1	48.2	61.9	72.6	79.3
E-4	0.6	1.2	2.6	4.3	8.6	14.0
E-5	14.4	28.0	49.4	68.2	92.4	99.1
E-6	0.8	2.8	6.3	10.4	14.6	19.3
E-7	5.9	26.3	48.2	65.1	77.4	85.9
E-8	0.5	1.5	2.7	4.1	5.9	7.6

Application of Central Composite Design: Central composite design was used for the preparation of a robust formulation by using different ranges of plasticizer and coating.

The applied design gave the predicted results according to the target made for the release. Following the target for the percentage, the release was made. Percentage release at 2 h < 25%. Percentage release at 6 h 40 to 60%. Percentage release at 12 >80%.

Formulation and Evaluation of Granules of Metformin Hydrochloride: Prepared granules of Metformin Hydrochloride were evaluated. Evaluation of granules is required for the determination of characteristics like the flow of granules, compressibility *etc.* The evaluation parameters were found within their acceptance range. Evaluations of granules of central composite design are shown in **Table 3**.

Formulation and Evaluation of Core Tablets: Prepared tablets were evaluated and evaluation parameters were finding within their acceptance range. Evaluation of core tablets gave the idea about the strength, appearance, weight variation.

NaCl: Because as compared to without NaCl formulation there is very low impact *i.e.* Release is only enhanced for first-time point 2 h. *etc.* Evaluation data of tablets of central composite design is shown in **Table 3**.

TABLE 3: EVALUATION DATA FOR GRANULES AND TABLETS BY CENTRAL COMPOSITE DESIGN

	Evaluation data for granules				Evaluation data for tablets			
Batch code	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose	Avg. hardness	Friability	Weight variation
F-1	0.5123	0.6249	1.2197	18.0188	30.6°	17.9	0.078	580 ± 5 mg
F-2	0.5029	0.6192	1.2312	18.7823	29.8°	16.8	0.089	555 ± 5 mg
F-3	0.5002	0.6182	1.2359	19.0876	28.9°	16.5	0.091	555 ± 5 mg
F-4	0.5129	0.6184	1.2056	17.0601	29.2°	17.1	0.068	555 ± 5 mg
F-5	0.5216	0.6394	1.2258	18.4235	30.8°	19.2	0.062	605 ± 5 mg
F-6	0.5121	0.6189	1.2085	17.2564	29.5°	16.2	0.092	555 ± 5 mg
F-7	0.5311	0.6382	1.2016	16.7815	27.6°	18.9	0.065	605 ± 5 mg
F-8	0.5296	0.6294	1.1884	15.8563	28.2°	19.4	0.059	605 ± 5 mg
F-9	0.5384	0.6349	1.1792	15.1992	30.1°	18.1	0.071	580 ± 5 mg
F-10	0.5223	0.6295	1.2052	17.0293	28.4°	17.8	0.069	580 ± 5 mg
F-11	0.5199	0.6249	1.2019	16.8026	30.3°	18.5	0.082	580 ± 5 mg
F-12	0.5302	0.6387	1.2046	16.9876	27.8°	18.8	0.063	605 ± 5 mg
F-13	0.5287	0.6257	1.1834	15.5026	29.4°	18.2	0.072	580 ± 5 mg
F-14	0.5293	0.6359	1.2013	16.7636	29.3°	19.5	0.059	605 ± 5 mg
F-15	0.5214	0.6198	1.1887	15.8760	27.1°	18.3	0.074	580 ± 5 mg
F-16	0.5183	0.6163	1.1890	15.9013	28.6°	16.7	0.092	555 ± 5 mg

Coating of the Core Tablets: Coating of the core tablets was done using gansons coater. One of the important things for the coating of the O-CDDS is how to avoid spray drying in case of volatile solvents of the coating solution for the preparation of a transparent film. If the spray drying occurred there are many chances of the formation of the hazy film. For the preparation of the transparent film, the important thing is the bed to the gun distance which should be closer (4-6 cm) to bed in case of volatile solvents like acetone, isopropyl alcohol (IPA) *etc.*

***In-vitro* Dissolution:** *In-vitro* dissolution was performed for the prepared O-CDDS and the percentage release of the drug gave the idea for the selection of factors that were taken for the optimization using central composite design.

The dissolution data of different batches of central composite design and marketed sustained-release tablets is given in **Table 4**. The marketed sustained-release tablets released approximately 80% of drugs at 6 h, so it is not able to give the

zero-order release which is required in case of lifelong diseases like diabetes mellitus.

TABLE 4: DISSOLUTION DATA OF DIFFERENT BATCHES OF CENTRAL COMPOSITE DESIGN

Batch code	2 h	4 h	6 h	8 h	10 h	12 h
F-1	14.0	29.3	43.2	54.6	66.1	74.6
F-2	6.1	15.9	25.7	34.3	44.4	52.6
F-3	29.6	52.8	71.7	98.2	99.4	100.0
F-4	18.5	36.9	51.7	66.2	81.1	99.8
F-5	4.8	13.7	21.7	30.3	41.6	56.9
F-6	14.1	28.2	41.0	52.7	67.4	94.9
F-7	30.6	54.1	72.1	80.9	90.0	94.5
F-8	11.4	26.4	40.0	52.9	63.9	73.1
F-9	14.5	31.9	44.8	58.3	69.3	78.4
F-10	24.3	48.4	63.4	79.4	89.9	96.2
F-11	10.7	24.2	36.5	49.4	59.2	68.9
F-12	11.2	28.2	41.5	55.4	67.1	74.2
F-13	8.6	21.1	31.9	44.2	54.6	64.4
F-14	17.2	36.8	52.9	66.2	77.3	82.9
F-15	18.3	36.9	52.7	66.0	76.3	85.4
F-16	14.4	29.4	42.3	54.2	65.8	91.8
Market tablet	46.4	68.2	83.5	91.4	96.3	98.3

Evaluation of Analytical Data Using JMP Software: JMP software was used for the evaluation of *in-vitro* dissolution data as the design was also applied using the same software. The data of *in-vitro* dissolution that is data of 2 h, 6 h, and 12 h was filled into the software for obtaining the results.

A prediction profiler and a contour profiler were obtained which are given in **Fig. 1** and **Fig. 2** respectively. The white space given in the contour profiler is the space in which the dissolution data will remain always as targeted. The P-value of less than 0.05 indicates that the model terms are significant. The values of the lack of fit model observed are given in **Table 5**.

TABLE 5: SUMMARY OF FIT

Parameters	Y1	Y2	Y3
R Square	0.993027	0.996597	0.953973
R Square Adj.	0.982567	0.991493	0.884933
Root Mean Square Error	0.987573	1.339702	5.49984
Mean of response	15.51875	45.81875	81.275

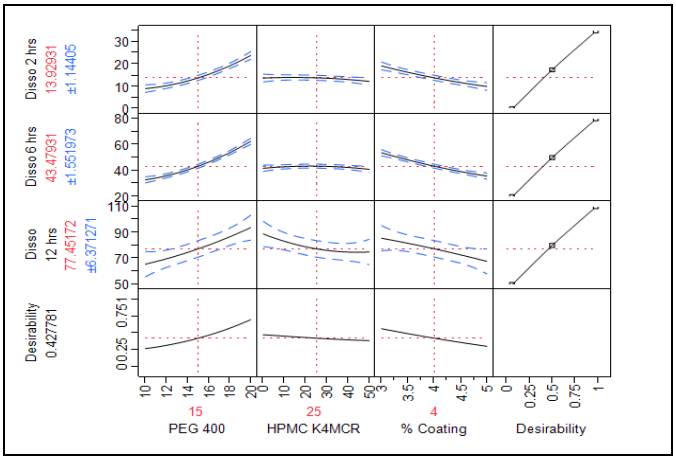

FIG. 1: PREDICTION PROFILER FOR CCD

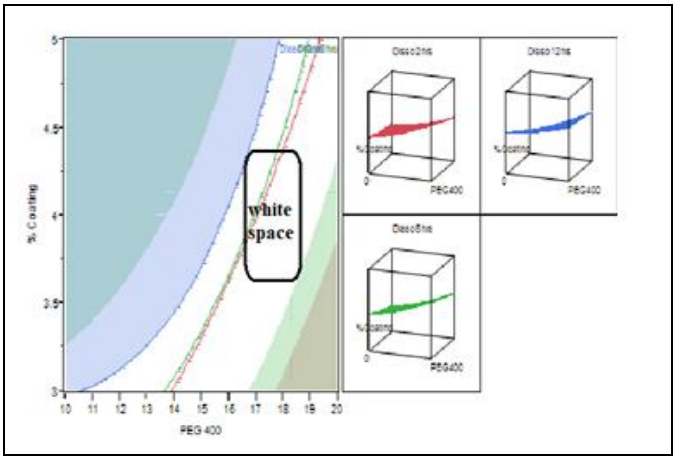

FIG. 2: CONTOUR PROFILER OF CCD

Comparison of Analytical Data with Marketed SR Tablets: Analytical data of prepared O-CDDS batch (F-4) was found linear as compared to the marketed SR tablets of Metformin hydrochloride. The comparison data is given in **Fig. 3**.

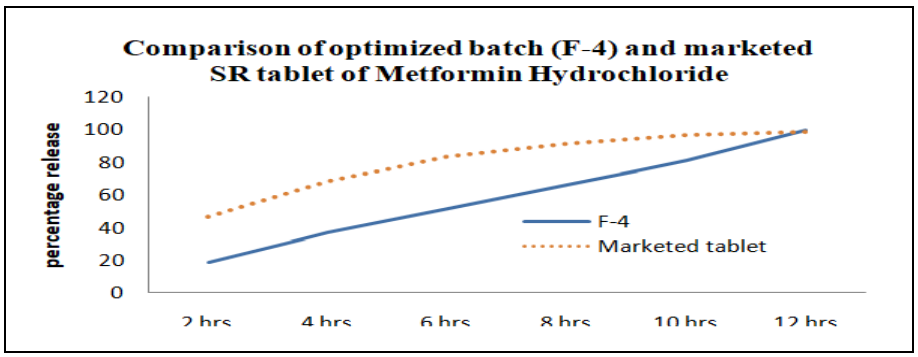

FIG. 3: COMPARISON DATA OF O-CDDS AND MARKETED SR TABLETS

Taking the Images of Delivery Orifice: Images of delivery orifice were taken using the polarizing optical microscope attached with the canon camera and the images were saved in the attached computer. The images are given in **Fig. 4**.

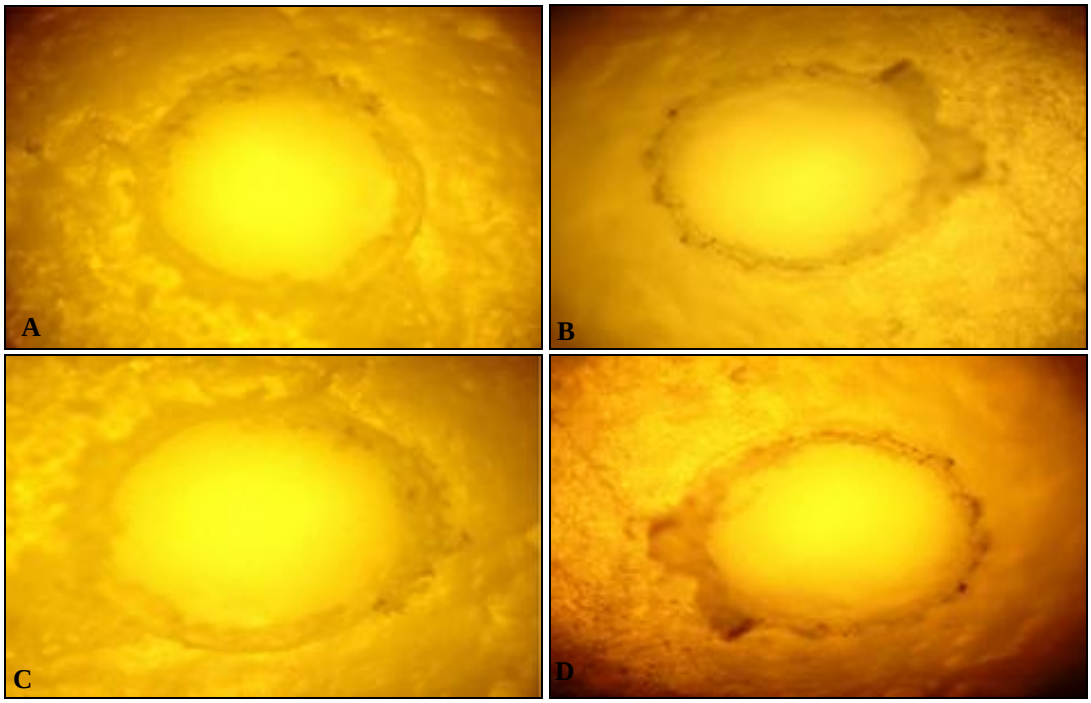

FIG. 4: IMAGES OF DELIVERY ORIFICE

Measurement of the size of the delivery orifice for the measurement of delivery orifice the images were taken using the optical polarizing microscope was used and the images were then opened into the software Image pro which gives the measurement of orifice size diameter. The observed orifice sizes of tablets A, B, C and D were found 158.5032, 152.9842, 162.1023 and 156.9849 respectively.

CONCLUSION: O-CDDS is a recent tool for solving the problem of controlled release of formulation and to provide a zero-order release profile. In the present study, O-CDDS of Metformin Hydrochloride was formulated for the controlled release of the drug.

The elementary osmotic pump of Metformin hydrochloride was made in the present study. On the basis of the experiments done during the screening design, it is concluded that hydrophobic plasticizer made the release very slow and 1 orifice was not successful for the prepared O-CDDS. Also, there was no use of osmogen in the prepared O-CDDS. So on the basis of screening design, the above factors were eliminated and further study was done using central composite design.

The response of the dissolution of 2 h (Y1), the response of dissolution of 6 h (Y2), the response of dissolution of 12 h (Y3) were taken. The formulation of batch F-4 was found best which has 50 mg of HPMC K_4M CR, 20% of PEG-400 in the coating and 5% of the coating. In this study, It is concluded that the O-CDDS give zero-order release as compared with marketed sustained release tablets which released more than 80% drug at 6 h.

The marketed tablets have poor control over the release of the drug as compared to O-CDDS. Thus, O-CDDS is a good way to avoid the multiple dosing and for the preparation of a controlled release tablet of Metformin hydrochloride which will give the therapeutic effect for the whole day.

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CONFLICTS OF INTEREST: The authors confirm that this research article content has no conflicts of interest.

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