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Design and statistical optimization of solubility modulated monolithic osmotic tablet of metformin hydrochloride (SCOT)

Rashmi Sharma[1*], Saroj Jain[1], Ravindra Tiwari[2] and Kirpashanker Tiwari[2]

[1]*Department of Pharmaceutics, Hindu College of Pharmacy, Sonepat, Haryana*
[2]*Product Development and Research, Ranbaxy Laboratories Ltd., Gurgaon, India*

ABSTRACT

This research paper deals with design, optimization and evaluation of SCOT of metformin hydrochloride. A full factorial design was employed to optimize the amount of solubility modulating agent (X_1) and % PEG in CA (X2) and % wt. build up (X_3) as independent variables that influence the drug release. SCOT tablets of metformin were prepared by wet granulation method and evaluated for cumulative % drug release at 2,8,16 hours as dependent variable. Fabricated SCOT tablets were evaluated for weight variation, thickness, hardness, friability, and in-vitro release studies. Sodium chloride as solubility modulating agent retards the drug release. The % wt. buildup had effect on drug release due to Increase in coating weight from (2-5%) which retards drug release due to increase in thickness of semi permeable membrane. The values of independent and dependent variables were subjected to least square fit analysis to establish a full model. The prediction profiler and counter plot was generated at the concentration of in dependent variables X_1(10.2 mg/tab), X_2 (5) and X_3 (3.5%) for maximized response. The drug release from developed formulation was found independent of pH and agitation intensity. The in-vitro release of fabricated osmotic tablet was compared with marketed osmotic and matrix tablet. The in-vitro release kinetics of fabricated osmotic tablet was found similar to marketed osmotic tablet as both followed zero-order release kinetics, While Matrix tablets exhibited Higuchi model.

Key words: Drug release, cellulose acetate, solubility modulating agent, Zero order drug release, osmotic tablet, SCOT

INTRODUCTION

Conventional drug delivery systems have little or no control over drug release and effective concentration at the target site. So, it is difficult to achieve and maintain the concentration of administered drug within the therapeutic range, leading to fluctuations in plasma drug levels. However, significant advances have been made in the development of drug delivery device that can precisely control the rate of drug release for an extended period of time. Several novel controlled drug delivery systems with many advantages have been developed in recent years. [5] Among these systems, the oral controlled drug delivery system has received greater attention since it is the most popular route of drug administration. [11]. Many designs are available to deliver the drug in controlled manner from dosage forms. Compared with other controlled release system. e.g. Matrix or reservoir system, The drawback of matrix-type delivery systems is their first-order drug delivery mechanism caused by changing surface area and drug diffusional path length with time. This drawback has been addressed by osmotic delivery systems, which maintain a zero-order drug release irrespective of the pH and hydrodynamics of the GI tract. Unlike matrix systems, reservoir

systems have a drug core coated with a rate controlling membrane to control the release.[3,6].Osmotic system utilize the principles of osmotic pressure for the delivery of drugs and drug release from osmotic system is independent of pH and other physiological parameters. This makes the osmotic drug delivery system one of the most interesting and widely applicable controlled release forms. [4] Different systems have been developed based on principle of osmotic pressure, including one chamber and multiple chamber systems. Currently two osmotically controlled delivery mechanisms that are widely used by the pharmaceutical industry are elementary osmotic pump (EOP) and push pull osmotic pump (PPOP). The EOP system is used for the freely soluble drug but not suitable for delivering those drugs having low aqueous solubility. The bilayer PPOP tablets were introduced in an attempt to overcome the limitation. [6,14].

Osmotic controlled drug delivery system is not influenced by different physiological factors with in the gut lumen and the release characteristic can be predicted easily from the drug and dosage form. Good product performance in osmotic system includes permeability of coating and drug release from the system. [12,4] Osmotic drug delivery system contains semipermeable membrane usually contains a plasticizer and pore former. [7,14] Metformin is freely soluble drug there we use sodium chloride as solubility modulating agent is used which helps to modulate the solubility of drug and retard the drug release. [15-20] Suggested that incorporating sodium chloride modulate the solubility of highly water soluble drug [13] .Thickness of tablet coating is extremely important as it affects the functionality of coating that means affect drug release, which is important parameter in extended release oral dosage forms. Based on the above information, in this study effect of varying ratio of cellulose acetate and PEG, thickness of coating on drug release and amount of solubility modulating agent required for the constant release of drug was investigated for extended period of time.

The present study relates to the controlled release dose formulation containing an anti-hyperglycemic drug for Diabetes mellitus, often simply referred as diabetes, a group of metabolic disease in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). To overcome the problem metformin is used as a first line drug of choice for the treatment of type 2 Diabetes in overweight and obese people and those with normal kidney function. Metformin works by suppressing glucose production. Metformin is freely soluble in water and practically insoluble in Acetone, ether and chloroform**.** Metformin has an oral bioavailability of 50–60% under fasting condition. Metformin HCl presents formulation challenges due to its inherently poor compressibility, high dose and high water solubility (> 300 mg/ml at 25 ºC). It belongs to class III of Biopharmaceutical Classification System (BCS) having high water solubility and low permeability[23]. The plasma protein binding of Metformin is negligible, as reflected by its very high apparent volume of distribution (300–1000 L after a single dose). Metformin has acid dissociation constant values (pKa of 2.8 and 11.5) which make it a stronger base than most other basic drugs with less than 0.01% unionized in blood. The average elimination half-life in plasma is 6.2 hour. [1] Because of the use of high dose and frequent dosing, controlled release formulations are necessary which deliver the API in controlled rate over a period of time. Osmotically controlled system formulated as once a day formulation reduces frequency of dose and side effects of drug and provide more patient compliance.

MATERIALS AND METHODS

Materials

Metformin hydrochloride (Venbury Ltd) was chosen as model drug for study; cellulose acetate (CA-398-10) was supplied by Eastman. Polyethylene glycol (Polyglycol 3350) selected as plasticizer was obtained from Clariant Products. Sodium chloride (Fisher Scientific) was used as solubility modulating agent. All other reagents were of analytical grade.

Experimental design

A number of preliminary experiments were conducted to determine the formulation and parameters by which the process resulted in single composition osmotic tablets of Metformin hydrochloride. A full factorial design was employed to systematically study the effect of solubility modulating agent (X_1) and % of PEG in cellulose acetate (X_2) and % wt. build up (X_3) on cumulative drug release at different hours (Y_1= at 2hr, Y_2= at 8hr, Y_3=16hr). In this design 3 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations (table.1). Response of all trials was analyzed using least square analysis with the help of JMP 11, Design-Expert software. [14]

Table-1: Selection of levels for independent variables

Levels	X_1	X_2	X_3
	Amount of sodium chloride	**% of PEG in CA**	**% wt. build up**
Low (-)	**10**	**1**	**2**
Medium (0)	**20**	**5**	**3.5**
High(+)	**30**	**9**	**5**

According to controlled release guidelines for extended release tablets the dissolution specifications were chosen as dependent variable (Table.2). Here three time points selected first time point to exclude dose dumping, second time point to ensure compliance with the shape of dissolution profile and last time point shows majority of active substance has been released. [31,32]

Table-2: Limits of dependent variable

Response Time points (hrs.)	Target Amount dissolved 1000-mg Tablet
Y_1 =2	**NMT 30%**
Y_2 =8	**45%-60%**
Y_3 =16	**NLT 90%**

Methods

The objective of this work was to study the effect of cellulose Acetate: PEG ratio, amount of sodium chloride and weight build up on drug release of Metformin Hydrochloride Osmotic Tablets. The designed tablets of Metformin hydrochloride were fabricated into three stages: first, the drug (Metformin HCl) and modulating agent (Sodium chloride) granules were prepared by wet granulation technique using PVP K30 as binder. Second, formed granules were compressed into core tablets by using suitable punching tools. Third, the formed core tablets were coated with varying ratios of cellulose acetate and PEG as semi permeable membrane.

Preparation of core tablet

As the Metformin Hydrochloride API flow and compressibility index are poor, wet granulation procedure was followed for the preparation of core tablet using Povidone (PVPK-30) as binder solution. Sodium chloride as solubility modulating agent and Magnesium stearate as lubricant. Direct compressible lactose (DCl) as used in extra granular material. The tablets were prepared by wet granulation technique using Rapid Mixer Granulator.
The formulae for different core tablet are given in table.3.

Table.3: Composition of Full factorial design formulations for SCOTs

Formulae for different core tablets.									
Ingredients	**F1** (mg/tab)	**F2** (mg/tab)	**F3** (mg/tab)	**F4** (mg/tab)	**F5** (mg/tab)	**F6** (mg/tab)	**F7** (mg/tab)	**F8** (mg/tab)	**F9** (mg/tab)
API	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**
PVPK30	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
Sodium Chloride	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
water	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**
Magnesium stearate	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
Direct Compressible lactose	**68**	**78**	**58**	**78**	**58**	**78**	**58**	**78**	**58**
Total weight (mg/tab)	**1200**	**1200**	**1200**	**1200**	**1200**	**1200**	**1200**	**1200**	**1200**
For Semipermeable Membrane									
Ratio of PEG in Cellulose Acetate	**95:5**	**99:1**	**99:1**	**91:9**	**91:9**	**99:9**	**99:9**	**91:9**	**91:9**
Acetone	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**
Water	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**
% weight gain	**3.5**	**2**	**2**	**2**	**2**	**5**	**5**	**5**	**5**
Total weight (mg/tab)	**1242**	**1224**	**1224**	**1224**	**1224**	**1260**	**1260**	**1260**	**1260**

The granules obtained from RMG were then milled using a 40G screen through Quadromill. The milled characterized granules were then lubricated with magnesium stearate and DCl added and then compressed using a tooling of around 21.3×10.40 mm. Standard oval punch using 16 station rotator tablet press (Make: cadmech, Ahmedabad, India). The blends prepared had good flow property and tablets were made without any problem.

Preparation of coating formulation

Cellulose acetate has been widely used to form a rate controlling membrane for osmotic systems. By choosing proper contents in coating composition the drug release can be controlled to desired levels. The core tablets with maximum hardness were chosen from the above prepared batches. The coating solution was prepared by dissolving Cellulose acetate in Acetone. The PEG (polyglykol 3350P) was dissolved in water and poured in Cellulose acetate and Acetone Solution and solution stirred until a clear solution was obtained. The coating equipment used was manufactured by (Ganscoater, make-Schneider electric) Coat was applied to core tablets with coating solution till weight gain of about 2%, 3.5%, and 5%. The parameters for coating were as follows:

Inlet Temperature: 25°C-°C,
Exhaust Temperature: 20°C-25°C,
Fluid delivery Rate: 10-18 gm. /min,
RPM of Pan: 10-13
Atomization air pressure: 1.2bar
Pattern Air Pressure: 1.8 bars

The formulae for different coating formulations as semipermeable membrane are given in table.1.

Characterization of granules

- **Bulk density (BD)**

10 gm. blend to be tested was taken. This powder blend was then poured in to the measuring cylinder. The powder was leveled without tapping. The bulk density was calculated using following formula:

Bulk density = Mass (gm.) / Bulk volume (ml)

- **Tapped Density (TD)**

For this cylinder was put in the holder of USP tapped density apparatus where it was tapped for 1000 taps. After 1000 tapes the final volume of powder was noted and tapped density was measured.

Tapped density = Mass (gm.) / Tapped volume (ml)

- **Carr's compressibility index**

The compressibility index of the powder blend was determined using following formula:

Compressibility Index = 100× (TD-BD) / TD

- **Hausner's ratio**

Hausner's ratio was calculated for characterization of flow of powder blend using following formula:

Hausner's ratio = TD / BD

Characterization of Tablets [8,9]

- **Weight variation test-**

Twenty tablets of coated and uncoated batches were randomly selected from each batch and individually weighed. The average weight and standard deviation of twenty tablets was calculated.

- **Hardness, Thickness and Friability**

Hardness of randomly selected Tablets was tested using hardness tester (Pharmatron, Dr. Schleuniger tablet tester 8M). Thickness of core tablet and coated tablets were measured using varnier caliper. 10 tablets from every batch were randomly selected.

Friability of 10 core tablets was carried out on a Roche Friabilator (Electro lab EF2 friabilator (USP) for 10 accurately weighed tablets.

- ***In-vitro* Dissolution study of core tablet**

Dissolution of core tablet was performed as per USP Basket method (# 40) at condition of 37°C ± 0.5°C in 6.8 phosphate buffers with a basket rotating at 100 RPM.

Creation of delivery orifice

Drilling of coated tablets was carried out on opposite side of surface of coated tablets to create an orifice of dimensions of 0.8 mm to 1mm with the help of mechanical drilling machine.

EVALUATION OF METFORMIN HYDROCHLORIDE SCOT TABLET

***In-vitro* dissolution study**

In-vitro drug release studies were performed as per USP Basket method at condition of 37°C ± 0.5°C in 6.8 phosphate buffers with a basket rotating at 100 RPM. Samples (5ml) were withdrawn at predetermine time intervals and replaced with equal volume of media. The concentration of Metformin released from the coated tablets was measured by UV absorption spectroscopy at 233 nm. The release studies were conducted in triplicate and parameters such as percentage cumulative drug release were calculated. [1]

CHARACTERIZATION OF OPTIMIZED FORMULATION [21]

Effect of pH

An osmotically controlled release system delivers its contents independent of external variables. The in vitro drug release of optimized formulation was carried out in pH 0.1 N HCl, Acetate buffer (pH 4.5) phosphate buffer (pH 6.8).

Effect of agitation intensity

In order to study the effect of agitation intensity of the release media, release studies of optimized formulation was carried out at various rotational speed i.e. 50,75,and 100 rpm in USP-I dissolution apparatus.

Release kinetics

In order to understand the mechanism and kinetics of drug release the results of *in-vitro* drug release study were fitted into various kinetic equations namely Zero order, (% drug release vs. t) first order,(% unreleased vs. t), higuchi matrix (% release vs. Square root of time) and Hixson Crowell model (cube root of drug percentage remaining in matrix vs. time),In order to define a model which will represent a better fit for the formulation, drug release data was further analyzed by Korsmeyer Peppas model used for the measure of primary mechanism of drug release. R^2 values were calculated for the linear curves obtained by regression analysis of optimized drug release plot. [22,10]

RESULTS AND DISCUSSION

4.1. Characterization of granules [8,9]

- **Bulk density (BD)**

The bulk density & taped density for formulation prepared by wet granulation technique were found to be in range of **0.542** to **0.568** gm. /cc & **0.642** to **0.674 gm/cc** the values obtained lies within acceptable range & with no significant difference found between values of tapped density and bulk density; results are shown in table.4. These results help in calculating % compressibility index of powder.

- **Compressibility index**:

Percent compressibility of powder mix was determined by Carr's index as shown in table.4. The percent compressibility index for formulations prepared by wet granulation technique was in range of 10.2 to 17.1 % respectively. All formulation showed good compressibility.

- **Hausener's ratio:**

Hausener"s ratio for the formulations prepared by wet granulation technique was found to be in range of 1.13 to 1.20 % shown in table.4. Both compressibility index & hausener"s ratio values showed that blends has good compressibility.

Characterization of tablets [8,9]

- **Weight uniformity**

Weight variation of the prepared tablet indicated no significant difference in the weight of individual tablet from the average value. Prepared tablet complies the weight variation test. [25,23]

➢ **Hardness, Thickness and Friability**

Hardness of the prepared tablets was observed within the range of 19.3±0.5 to 22.4±0.4 kg/cm2. Friability of all tablets was found below 1%. Thickness of all core tablets were found in the range of 6.21±0.5 to 6.50±0.05mm and coated tablets thickness were 6.49±0.1to 6.77±0.2 mm respectively. [25] The values of various evaluation parameters for core and coated tablets are given in table. 5.

Table.4: Values of various parameters for characterization of granules

Formulation Code	Bulk Density (g/cm²)	Tapped Density (g/cm²)	Hausner'sRatio %	Carr's Index (%)
	n=3			
F1	**0.561**	**0.674**	**1.2**	**16.8**
F2	**0.554**	**0.658**	**1.2**	**17.1**
F3	**0.542**	**0.654**	**1.2**	**15.9**
F4	**0.565**	**0.64**	**1.13**	**11.8**
F5	**0.548**	**0.642**	**1.17**	**14.7**
F6	**0.568**	**0.632**	**1.11**	**10.2**
F7	**0.547**	**0.656**	**1.19**	**16.7**
F8	**0.559**	**0.649**	**1.16**	**13.9**
F9	**0.552**	**0.659**	**1.19**	**16.3**

Table.5: The values of various evaluation parameters for core and coated tablets

Formulation code	weight variation n=20 Uncoated/coated	Thickness(mm) n=10		Hardness (Kg/cm²) n=5 uncoated	%Friability n=10	% wt. buildup of CA
		Uncoated	**coated**			
F1	**Complies**	**6.30±0.1**	**6.55±0.1**	**22.4±0.4**	**0.033**	**3.50%**
F2	**Complies**	**6.50±0.05**	**6.57±0.1**	**20.4±0.4**	**0.066**	**2%**
F3	**Complies**	**6.48±0.2**	**6.69±0.1**	**19.5±0.5**	**0.083**	**2%**
F4	**Complies**	**6.28±0.8**	**6.49±0.1**	**20.5±0.5**	**0.056**	**2%**
F5	**Complies**	**6.44±0.2**	**6.63±0.1**	**22.1±0.2**	**0.017**	**2%**
F6	**Complies**	**6.21±0.5**	**6.68±0.1**	**19.3±0.5**	**0.049**	**5%**
F7	**Complies**	**6.41±0.5**	**6.70±0.1**	**20.5±0.5**	**0.054**	**5%**
F8	**Complies**	**6.36±0.5**	**6.77±0.2**	**20.6±0.6**	**0.068**	**5%**
F9	**Complies**	**6.46±0.4**	**6.73±0.1**	**22.6±0.2**	**0.072**	**5%**

***In-vitro* Dissolution study of core tablet**

The core tablet shows complete drug release in 15 minutes as shown in fig.1.

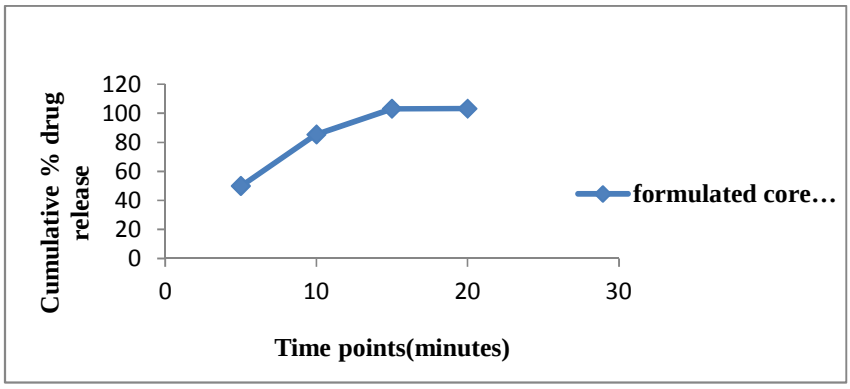

Fig.1: *In-vitro* Dissolution study of core tablet

***In-vitro* Dissolution study of coated tablets**

The results of *in-vitro* release of Metformin hydrochloride from different factorial formulations CAT1 to CAT9 is shown in table.4. Undrilled tablet dissolution shows cumulative drug release 14% in 20th hour. The optimized formulation from DOE trials was determined by similarity factor, and was found to be F5 having f_2 value 53.6.

Table.6: Percentage drug release profile of screening batches [Media-6.8 phosphate buffer]

factor	Level								
% of PEG in CA	95:05	99:01	99:01	91:09	91:09	99:01	99:01	91:09	91:09
Amt of Nacl	20	10	30	10	30	10	30	10	30
%wt Build up	3.50%	2%	2%	2%	2%	5%	5%	5%	5%
TimePoints (hrs.)	Cumulative % Drug release								
Batch no.	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	5.6	12.0	5.7	4.7	9.3	3.9	0.6	2.6	5.2
2	9	21.0	10.0	9.0	12.0	5.9	1.0	3.0	6.0
3	11.2	29.7	13.8	15.9	18.0	7.9	1.2	4.8	8.5
4	16.4	36.2	16.8	21.7	21.7	11.2	1.4	11.5	10.9
6	23.8	65.3	27.0	34.4	34.6	22.0	1.6	14.9	17.0
8	36.0	88.0	42.0	43.0	44.0	36.0	2.0	17.0	22.0
10	47.6	90.0	56.0	52.8	52.8	39.4	5.2	29.5	28.5
12	55.2	94.4	71.2	70.7	70.7	44.4	16.0	34.9	39.9
16	65.0	105	91.0	89.0	99.0	52.0	21.0	47.0	44.0
20	89.5	105.4	94.9	97.3	102.0	56.2	60.3	56.8	58.5

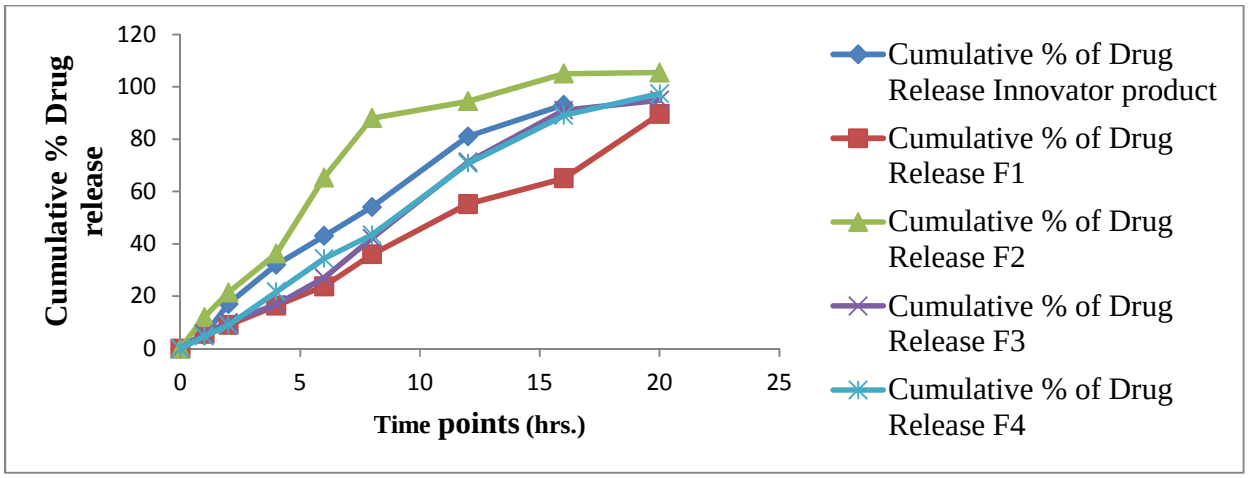

Fig-2: *In-vitro* release of Metformin hydrochloride from F1 to F4 formulation with Reference

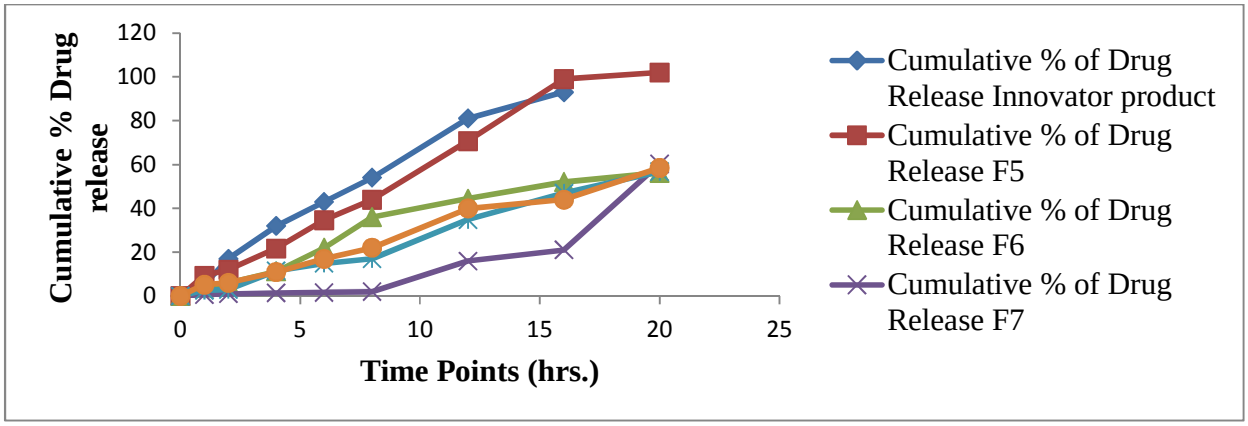

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Fig-3: *In-vitro* release of Metformin hydrochloride from F5 to F9 formulation with reference

4.2. Statistical Analysis

Experiments were carried out to determine the mathematical relationship between the factors acting on the system and the response of the system. The statistical evaluation of experimental outcomes was processed to find the optimum levels of amount of sodium chloride, % of PEG in cellulose acetate and % weight build up that would provide controlled release of Metformin hydrochloride form the formulations. Using regression analysis model equations were obtained for responses (dependent variable) is as follows. [14]

$$Y= \beta_o- \beta_1X_1- \beta_2X_2 +\beta_3X_3 +\beta_{12}X_1*X_2 + \beta_{13}X_1*X_3 +\beta_{23} X_2*X_3 \quad (1)$$

Where, Y is the dependent variable, β_o is the arithmetic mean response of the nine runs, and β_1 is the estimated coefficient for Factor X_1. β_2 is the estimated coefficient for Factor X_2. B_3 is the estimated coefficient for factor X_3. The main effects (X_1, X_2 and X_3) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1*X_2) show how the response changes when two factors are simultaneously changed. The equation represents the quantitative effect of factors (X_1, X_2, and X_3) upon the responses (Y_1, Y2 and Y_3). The response clearly indicates that the Y_1, Y_2 and Y_3 are strongly dependent on the selected independent variables. A mathematical relationship in the form of quadratic equations for cumulative % drug release at different time hours are as follows.

$$Y_1= 8.44 - 4.62(X_1)-6.87(X_2) -1.12(X_3) +1.62(X_1*X_2) +0.87(X_1*X_3) +2.62(X_2*X_3) \quad (2)$$

$$Y_2= 36.66 – 17.5(X_1) +5.25 (X_2) - 9.25 (X_3) +5.5(X_1*X_2) -2(X_1*X_3) +10.75 (X_2*X_3) \quad (3)$$

$$Y_3= 68.11-27.5(X_1) + 1.25 (X_2) - 4.76 (X_3) +3.25 (X_1*X_2)-3.75 (X_1*X_3) + 6.5 (X_2*X_3) \quad (4)$$

Where Y_1,Y_2,Y_3 drug release at 2 hr. ,8 hr. , 16 hr. and X_1 = amount of sodium chloride (mg/tab), X_2 = % PEG in cellulose acetate film, X_3 = % weight buildup of cellulose acetate film.

The values of correlation coefficient (R^2) for equations were found to be at 0.98,1 and 1 respectively. R^2=1, indicating good fit, shown in summary of fit table-7. Positive or negative signs before a coefficient in quadratic models indicate a synergistic effect and an antagonistic effect for the factor. The data clearly indicate that the dependent variables are strongly depending on independent variable.

As the amount of solubility modulating agent increased (NaCl), % cumulative drug release decreased.

This is because saturated solution of sodium chloride modulates the solubility of metformin (because of saturation solubility drug release decrease). Similar to sodium chloride the % weight build up affects the drug release due to increased resistance of membrane to water diffusion. As weight buildup increases drug release decreases. And % PEG in cellulose acetate shows less effect on drug release.

4.3. ANOVA study

Evaluation and interpretation of research findings are important and the p value serves a valuable purpose in these findings. The coefficient of X_1, X_2 and X_3 were found to be significant at $P < 0.05$, hence confirmed the significant effect of both the variables on the selected responses. Overall all independent variable caused significant change in response. ANOVA and multiple regression analysis were done using JMP design expert software. Adequacy and good fit of the model was tested using analysis of variance (ANOVA) as shown in Table.7 & 8. The multiple correlation coefficient (R^2) and sum of square, mean square, and f ratio are provided by JMP Design-Expert software. [17,26] To demonstrate graphically the effect of X_1, X_2 and X_3 prediction profiler (fig.4) and contour plot (fig.5) was obtained to find an optimized formulation within the factorial space.

Table-7: Summary of fit

Selected response	R^2	p-value	RMSE	R^2. adj	Mean of response
% DR at 2 hr.	**0.98**	**0.06**	**1.798**	**0.9**	**8.44**
% DR at 8 hr.	**1**	**0.005**	**2.061**	**0.99**	**36.66**
% DR at 16 hr.	**1**	**0.005**	**2.538**	**0.99**	**68.11**

Table-8: Results of ANOVA of full Factorial design for % DR of Metformin hydrochloride (SCOT).

% DR at 2 hr.	Source	DF	Sum of Squares	Mean Square	F Ratio
	Model	**6**	**269.75**	**44.9583**	**13.8927**
	Error	**2**	**6.47222**	**3.2361**	**Prob > F**
	C. Total	**8**	**276.2222**		**0.0687**
% DR at 8 hr.	**Source**	**DF**	**Sum of Squares**	**Mean Square**	**F Ratio**
	Model	**6**	**4553.5**	**758.917**	**178.5686**
	Error	**2**	**8.5**	**4.25**	**Prob > F**
	C. Total	**8**	**4562**		**0.0056***
% DR at 16 hr.	**Source**	**DF**	**Sum of Squares**	**Mean Square**	**F Ratio**
	Model	**6**	**6778**	**1129.67**	**175.2931**
	Error	**2**	**12.8889**	**6.44**	**Prob > F**
	C. Total	**8**	**6790.889**		**0.0057***

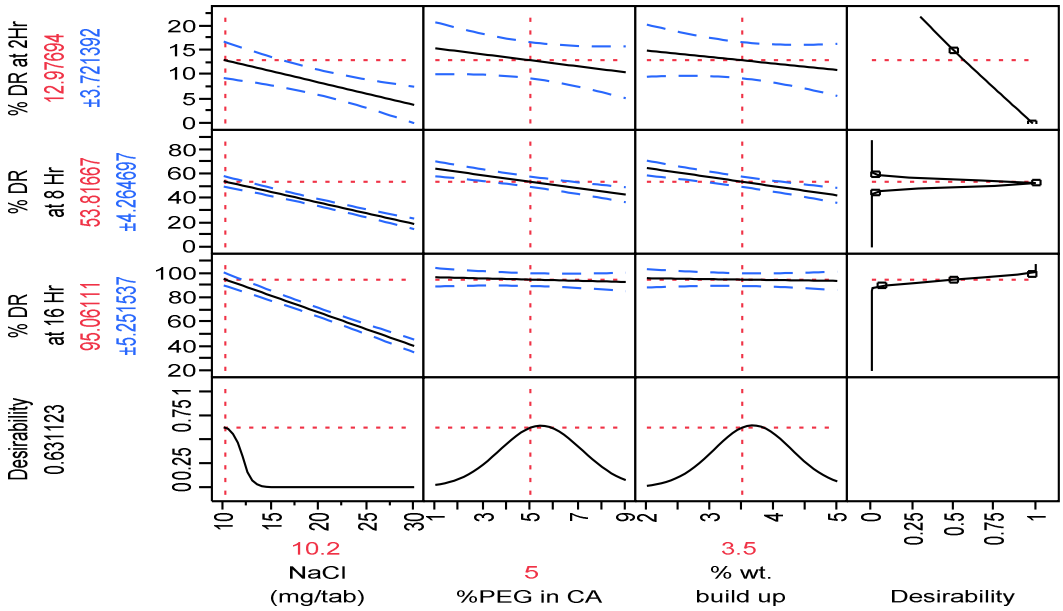

Fig.4: Prediction Profiler

Prediction profiler shows:

- % drug release was decreased by increasing the amount of sodium chloride from (10-30) in the formulation
- Increase in % weight build up from (2-5%) reduces drug release due to increase in thickness of semi permeable membrane which retard the release of drug.
- Increase in %PEG in CA slightly decreases drug release.

HorizVert	Factor	Current X		
	NaCl (mg/tab)	10.222		
	%PEG in CA	5		
	% wt. build up	3.5		
Response	**Contour**	**Current Y**	**Lo Limit**	**Hi Limit**
% DR at 2Hr	11.25	12.966769	.	30
% DR at 8 Hr	45	53.778167	45	60
% DR at 16 Hr	69	95.000611	85	.

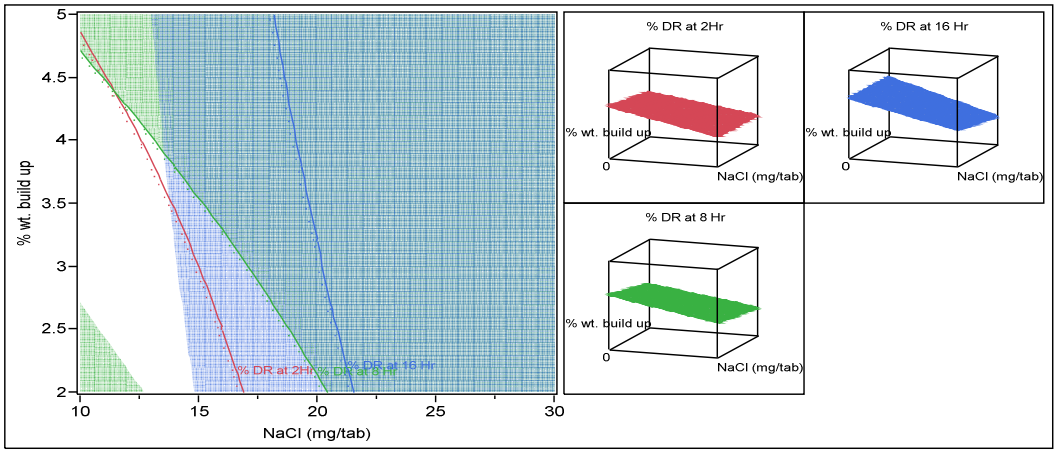

Fig.5: Contour Profiler

The contour plot was plotted between the amount of sodium chloride and % wt. build up shown in fig.5

- On the basis of desirability function best formulation was predicted by model using Sodium chloride (10.2mg) and % of PEG in CA (5%) weight build up (3.5%).
- Predicted drug release (response) of optimized formulation at 2hr =12.9 %, at 8 hr.= 53.7%,at 16 hr. = 95%

OPTIMIZED FORMULATION

The optimized formulation was obtained by applying limits of specification (goal) on dependent variable (response) at three time interval. On the basis of desirability function best formulation was predicted by model using amount of Sodium chloride (10.2mg) and % of PEG in CA (5%) weight build up (3.5%) and Predicted drug release (response) of optimized formulation at 2hr =12.9 %, 8 hr.= 53.7% and 16 hr. = 95%. For confirmation, the above optimum formulation was prepared and evaluated for cumulative % drug release. The resultant experimental values of responses were quantitatively compared with the predicted values to calculate the percentage prediction error. The experimental values of cumulative % drug release were found in close agreement with the predicted values.

CHARACTERIZATION OF OPTIMIZED FORMULATION

Effect of PH

Release kinetics of optimized formulation was conducted according to pH change method to study the effect of pH on drug release. The release media was pH 0.1 N HCl, Acetate buffer (pH 4.5) phosphate buffer (pH 6.8). Fig.6 shows release of Metformin from optimized formulation and it is clearly evident that the release profile is similar in all media, demonstrating that the developed formulation shows pH independent release.

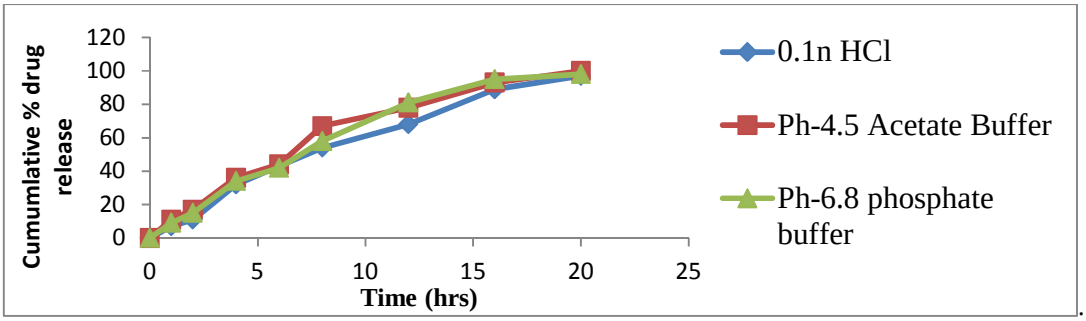

Fig.-6: Effect of pH on drug release from optimized batch F10

Effect of agitation intensity

The release profile of metformin ER is fairly independent of agitation intensity of release media and hence. It can be expected that the release from developed formulation will be independent of hydrodynamic conditions of the body. The effect of agitation intensity on drug release from optimized batch F10 is shown in fig.7.

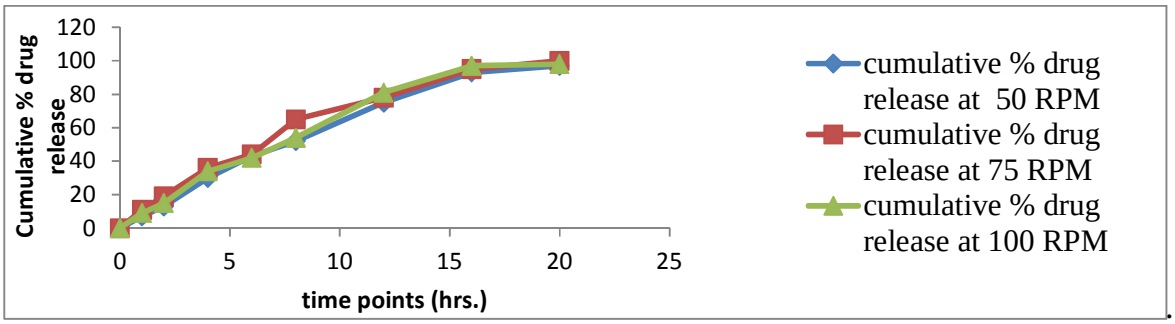

Fig.-7: Effect of agitation intensity on drug release from optimized batch F10

4.4. Release Kinetics

In order to understand the mechanism and kinetics of drug release of optimized batch F10 *in-vitro* drug release study. The various kinetic equations were namely Zero order (% drug release vs. t), first order (log % unreleased vs. t), higuchi matrix (% release vs. square root of time) and Hixson Croxwell model were fitted. The % drug release predicted by model fitting vs. time points is shown in fig.8. The values of R^2, K and n are shown in Table.9.

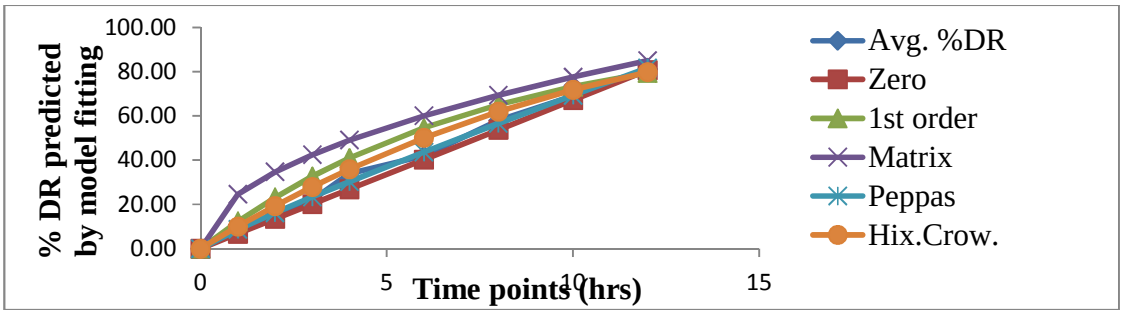

Fig.-8: % drug release predicted by model fitting vs. time points

Table.9: Kinetics of optimized formulation (F10), marketed matrix and marketed osmotic tablet

Formulation	Zero order	First order	Higuchi Matrix	Korsmayer-Peppas	Hixson-croxwell	Best fit model
F10 (optimized formulation)	R^2=0.994 K=6.712	R^2=0.978 K= -0.131	R^2=0.935 K=24.51	R^2=0.993 n=0.90 K=8.63	R^2= 0.988 K=0.034	Zero order
Matrix tablet (marketed)	R^2= 0.900 K =10.91	R^2= 0.993 K= -0.344	R^2=0.997 K=34.08	R^2= 0.997, n= 0.50 K= 34.14	R^2= 0.991 K = 0.074	Higuchi Matrix
Osmotic tablet (marketed)	R^2 = 0.973 K= 9.47	R^2= 0.827 K= -0.182	R^2=820 K= 26.18	R^2=0.954, n=1.23 K=5.71	R^2 =0.877 K =0.047	Zero order

COMPARISON WITH MARKETED FORMULATION [28]

The comparative evaluation of marketed matrix, marketed osmotic, and fabricated osmotic pump tablets for controlled delivery of metformin results that. The fabricated osmotic tablet, have similar drug release to the marketed product (Actomet XR). The rate shows drug release from matrix tablets (polymer matrix) was different from that of osmotic tablet because type of pore forming agents and solubility modulating agent also influenced the drug release. [29] The similarity factor was determined by comparing release profile of marketed osmotic tablet and formulated osmotic tablet. Similarity factor (***f2***) of optimized formulation (F10) was 58.3. [30] Analysis of in vitro

data revealed zero-order release kinetics for fabricated (R^2 - 0.994) and marketed osmotic tablets (R^2 - 0.973), while Matrix tablets exhibited Higuchi matrix model (R^2-0.997) as shown in table.9.The comparison of fabricated, marketed osmotic and matrix tablet is shown in fig.9.

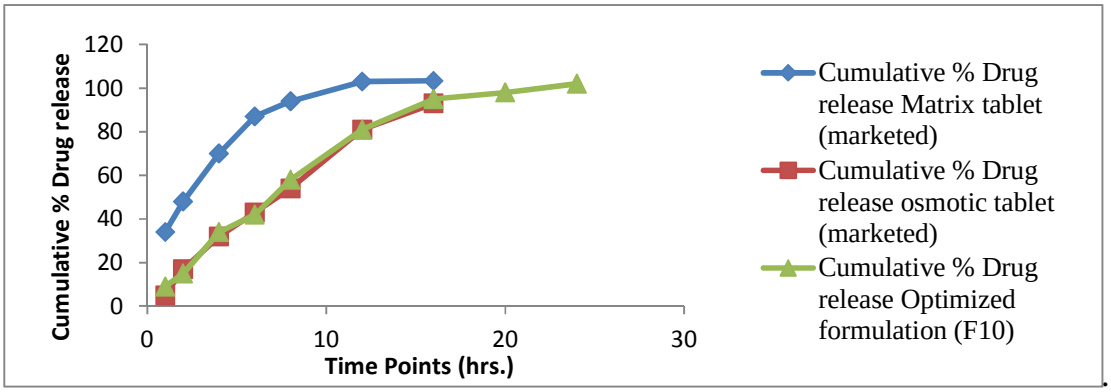

Fig.9: Cumulative % drug release of optimized formulation marketed osmotic and matrix tablet formulation

DISSOLUTION PROFILE OF ACTUAL VS. PREDICTED.

The dissolution data predicted by model for optimized formulation was compared with dissolution data obtained by fabricated osmotic tablet. The dissolution data of actual was found similar to the predicted by model. It is shown in fig.10.

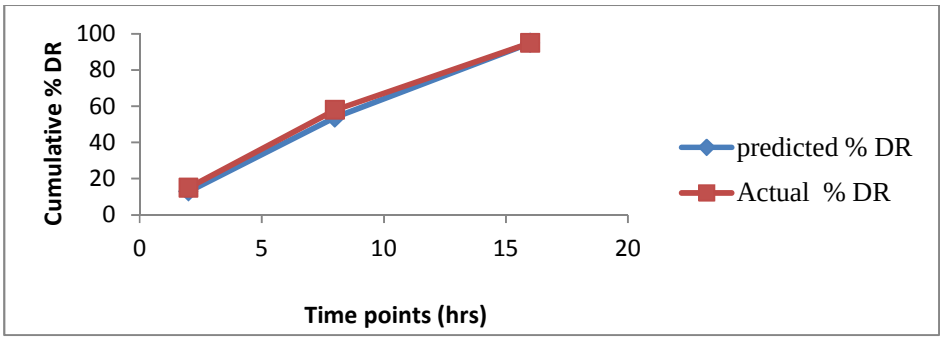

Fig.10: Dissolution data of Actual vs. predicted by the model

CONCLUSION

Single composition osmotic tablets coated with cellulose acetate as a semi permeable membrane and core containing solubility modulating agent have been developed for Metformin hydrochloride. The desired zero order release profile was obtained by optimizing concentration of solubility modulating agent, % of PEG in CA and % weight gain. Drug release decrease with the amount of sodium chloride as solubility modulating agent (10-30) increased due to the increased saturation solubility. Similar to the sodium chloride the % weight build up (2-5) affects the drug due to the increased resistance of membrane to water diffusion, when % wt. buildup of coating increases in formulation it decreases the drug release. Different ratio of coating formulation containing CA: PEG (1-9) had minor effect on drug release. For the predicted drug release our formulation should contain % wt. build up in range of 2% to 3%. The optimized formulation displayed similar drug release profile to the marketed formulation of osmotic tablet.

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