EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 1
Issue: 2
252-272
Year: 2014

FORMULATION, EVALUATION AND OPTIMIZATION OF ORO-DISPERSIBLE TABLET OF METFORMIN HYDROCHLORIDE

Rahil G. Bhura*, Nilesh Patel, Mehul B. Vyas, Dr. Samir K. Shah

Sardar Patel College of Pharmacy, Department of Pharmaceutics, Vidyanagar Vadatal Road, Bakrol, Anand.

Article Received on 05/08/2014 **Article Revised on 30/08/2014** **Article Accepted on 23/09/2014**

***Correspondence for Author**

Rahil G. Bhura,
Sardar Patel College of Pharmacy, Department of Pharmaceutics, Vidyanagar Vadatal Road, Bakrol, Anand.

ABSTRACT

Aim of present work was to provide quick onset of action due to rapid dissolution and disintegration of tablet and to prepare and evaluate orodispersible tablet of Metformin Hydrochloride by direct compression method. In current research, orodispersible tablet was prepared by using different super disintigrants like crosspovidone (CRP), sodium starch glycolate (SSG) and cross carmallose sodium (CCS). The formulations were prepared by using direct compression method. Nine batches were prepared as per 3^2 factorial design, to investigate the combined effect of independent effect of variables (X_1= amount of cross carmallose sodium and X_2= amount of crosspovidone) on dependent variables (disintegration time and % drug release release in 10 min). The prepared fast dissolving tablets were evaluated for various physicochemical parameters, such as weight variation, hardness, thickness, friability, disintegration time, wetting time, % drug content and % in vitro drug release to optimize the formula. In preliminary trials two super disintegrants cross carmellose sodium and cross povidone were found more effective as compared to sodium starch glycolate. 3^2factorial design results showed that amount of cross carmellose sodium and amount cross povidone had significant effect on disintegration time and % drug release. Out of all nine batches batch F5 (cross povidone 30 mg and cross carmellose sodium 30 mg) was selected as optimized batch with lower disintegration time (10.15 sec) and % drug release (93.28%). So from this work it was concluded that orodispersible tablets of metformin hydrochloride were prepared successfully.

KEYWORDS: Orodispersible tablet, Metformin Hydrochloride, Direct compression, Supurdisintegrants.

INTRODUCTION [1-18]

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action or both. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Thus, diabetes covers a wide range of heterogeneous disease. Type 1 diabetes is characterized by a lack of insulin production. Without daily administration of insulin, type 1 diabetes is rapidly fatal. Type 2 diabetes results from the body's ineffective use of insulin. About 90% of people with diabetes around the world have type 2. It is largely the result of excess body weight and physical inactivity [1]. Solid dosage forms like tablet and capsule are most popular and preferred drug delivery system because they have high patient compliance, relatively easy to produce, easy to market, accurate dosing and good physical and chemical stability. Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. In fact, the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore, a fundamental understanding of various disciplines, including GI physiology, Pharmacokinetics, Pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, the scientific frame work required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects. [4,5,6]

1. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug,
2. The anatomic and physiologic characteristics of the GIT and
3. Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

Metformin is an anti hyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral anti hyperglycemic agents. Metformin is usually well tolerated. The most common side-effect is minor gastrointestinal disturbance, which is often self-liminting or minimized by lowering the dose. So here selecting this drug as a model an attempt has been made to prepare oro-dispersible tablet of Metformin HCl which provide convenience of tablet formulation and allowing easy swallowing as of liquid formulation as well as to provides quick onset of action and due to rapid dissolution it may improve bioavailability also[15-18].

MATERIALS

Metformin HCl was obtained as a gift sample from Orbit Pharmaceuticals Ltd., Ahmedabad. Cross Carmalose sodium, Sodium Starch Glycolate, Cross povidone, Mannitol, Talc and MCC PH-102 were provided by Orbit Pharmaceuticals Ltd., Ahmedabad.

METHODOLOGY [20-45]

Method of preparation for tablets

Direct compression [42, 43]

This method consists of directly compressing blend, which consists of an excipient, and an active ingredient. The excipient consists of a disintegrating agent and one soluble diluent selected from polyols having less than 13 carbon atoms. Polyols most commonly used are xylitol, sorbitol, mannitol, and maltitol. Directly compressible form or various ratios of compressible and powder form of polyol used in these methods. Disintegrating are used Cross povidone, Cross caramellose sodium and Sodium starch glycollate. In addition to these ingredients, sweeteners and lubricants are incorporated in the formulation.

EVALUATION PARAMETERS [44]

Pre-compression parameters

Angle of repose

Angle of repose will be determined using funnel method. The blend will be poured through funnel that can be raised vertically until a maximum cone height (h) will be obtained. Radius of the heap (r) will be measured and angle of repose will be calculated using the formula.

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

Where, θ is the angle of repose, h is height of pile, r is radius of the base of pile.

BULK DENSITY

Apparent bulk density (ρ_b) will be determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of powder (M) will be determined. The bulk density will be calculated using the formula

$\rho_b = M/ V_b$

TAPPED DENSITY

The measuring cylinder containing known mass of blend will be tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and weight (M) of the blend will be measured. The tapped density (ρ_b) will be calculated using the following formula

$\rho b = M/ V_t$

CARR'S OR COMPRESSIBILITY INDEX

The simplest way of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility. The compressibility index of the granules will be determined by Carr's compressibility index (I), which is calculated by using the following formula

$I = (V_b – V_t) \times 100/ V_b$

HAUSNER'S RATIO

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula:

Hausner's ratio = ρ_t/ ρ_b

Where ρ_t is tapped density and ρ_b is bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

POST COMPRESSION PARAMETER

THICKNESS

Tablet thickness will be measured using a simple procedure. Tablets will be taken and their thickness will be measured using Vernier calipers.

HARDNESS

It will be the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing

strength of the tablet will be measured using Pfizer hardness testers. An average of three observations is reported.

UNIFORMITY OF WEIGHT

I.P. procedure for uniformity of weight will be followed, twenty tablets will be taken and their weight will determined individually and collectively on a digital weighing balance. The average weight of one tablet will be determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

DISINTEGRATION TIME

The test will carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at37ºC ± 2ºC will be used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus will be measured in seconds.

IN-VITRO DRUG RELEASE

The development of dissolution methods for ODTs will be comparable to the approach taken for conventional tablets, and practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for ODT much in the same way as their ordinary tablet counter parts. The USP 2 Paddle apparatus will be used for this purpose which will be the most suitable and common choice for orally-disintegrating tablets, with a paddle speed of 50 rpm commonly used. Typically the dissolution of ODT is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to obtain a profile. The USP 1 Basket apparatus may have certain applications but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles.

FRIABILITY TEST

Friability of the tablets will be determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets will be placed in the friabilator and will be subjected to 100 revolutions. Tablets will be de dusted using a soft muslin cloth and reweighed.

The friability (f) is taken by the formula.

$f = (W- W_0 / W) \times 100$

Where, W_0 = weight of the tablets before the test

W = the weight of the tablet after the test.

IN-VITRO DISPERSION TIME TEST

To determine dispersion time 10 ml measuring cylinder will be taken in which 6 ml distilled water will be added and tablet will be dropped in it. Time required for complete dispersion will be determined.

WETTING TIME

Five circular tissue papers of 10 cm diameter will be placed in a Petri dish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water soluble dye, will be added to petri dish. A tablet will be carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet will be noted as a wetting time.

WATER ABSORPTION RATIO

A piece of tissue paper folded twice will be placed in a small Petri dish containing 6 ml of water. A tablet will be put on the paper & the time required for complete wetting was measured. The wetted tablet will be then weighed. Water absorption ratio (R), will be determined using following equation,

$R = 100 \text{ x } W_a – W_b / W_b$

Where,

W_b = Weight of tablet before water absorption

W_a = Weight of tablet after water absorption.

DRUG CONTENT

Five tablets were weighed individually and powdered. The powder equivalent to 10 mg of Metformin hydrochloride was weighed and extracted in phosphate buffer pH 6.8 (100 ml) and the concentration of drug was determined by measuring absorbance at 233nm by UV spectrophotometer.

OPTIMIZATION OF FORMULA

Different batches will be prepared and best batch will be evaluated.

FACTORIAL DESIGN

- 3^2 Factorial statistical design with 2 factors, 3 levels, and 9 runs was selected for the optimization
- The independent and dependent variables are listed in Table 1.

Table 1: Design coded table

Independent variable	Levels		
Transformed values	-1	0	1
X_1=con of Cross Carmalose sodium	20	30	40
X_2=con of Cross povidone	20	30	40
Dependent variables	X_1=Dissolution time X_2=Disintegration time		

STABILITY STUDY [45]

The oro-dispersible tablets will be packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1 °C

(ii) 50 ± 1°C

(iii) 37 ±1 °C and RH 75% ± 5%

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Vissual defects, Hardness, Friability, Disintegrations, Dissolution and drug content etc). The data obtained were fitted into first order equations to determine the kinetics of degradation. Accelerated stability data were plotting according Arrhenius equation to determine the shelf life at 25°C.

RESULT & DISCUSSION

Physical Properties of Drug

Table 2: Physical properties of drug

Parameters	Values
Bulk Density	0.444 gm/cm^3
Tapped Density	0.625 gm/cm^3
% Compressibility	28.96 %
Housner Ratio	1.40
Angle of repose θ	32.82

PRELIMINARY STUDY FOR SELECTION OF SUPERDISINTEGRANTS

In preliminary study of selection of superdisintegrants, 9 trial batches of different concentrations of superdisintegrants were prepared. All the trial batches were evaluated for hardness, disintegration test and wetting time. The results from preliminary trail batches indicated that CCS and CRP showed more effective and enhanced disintegration property than SSG. The quicker disintegration time may be attributed to faster water uptake by the tablet. In this liquid is drawn up or "wicked" in through capillary action and rupture the inter-particulate bonds causing the tablet to break apart. Out of four the three super disintegrants (CCS and CRP) from the preliminary studies were selected for further studies.

PRELIMINARY TRAIL BATCHES

Table 3: Preliminary trail batches

Material(mg)	A1	A2	A3	A4	A5	A6	A7	A8	A9
Metformin HCl	250	250	250	250	250	250	250	250	250
CCS	10	25	40	-	-	-	-	-	-
SSG	-	-	-	10	25	40	-	-	-
CRP	-	-	-	-	-	-	10	25	40
Mannitol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	5	5	5	5	5	5	5	5	5
Mg. Stearate	5	5	5	5	5	5	5	5	5
MCC PH-102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total	500	500	500	500	500	500	500	500	500

EVALUATION OF PRELIMINARY TRAIL BATCHES

Table 4: Evaluation of preliminary trail batches

Evaluations	A1	A2	A3	A4	A5	A6	A7	A8	A9
Hardness Kg/cm^3 (±S.D)	2.72 ±0.51	2.89 ±0.37	3.10 ±0.62	2.93 ±0.21	3.14 ±0.16	2.86 ±0.42	3.06 ±0.29	2.80 ±0.18	2.96 ±0.13
Disintegration time(sec)(±S.D)	25.54 ±1.06	20.33 ±.98	15.84 ±2.08	35.56 ±1.67	29.48 ±2.41	25.31 ±3.03	27.74 ±2.66	22.91 ±1.74	18.51 ±2.19
Wetting time(sec)(±S.D)	45.66 ±2.07	40.09 ±1.05	36.34 ±2.24	48.49 ±1.73	39.36 ±0.88	43.26 ±2.31	41.38 ±1.52	47.51 ±1.92	40.11 ±2.17

COMPOSITION OF FORMULATION BATCHES

Table 5: Composition batches

Material(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin HCl	250	250	250	250	250	250	250	250	250
CCS	20	20	20	30	30	30	40	40	40
CRP	20	30	40	20	30	40	20	30	40
Mannitol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	5	5	5	5	5	5	5	5	5
Mg. Stearate	5	5	5	5	5	5	5	5	5
MCC PH-102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total	500	500	500	500	500	500	500	500	500

EVALUATION PARAMETERS

PRE-COMPRESSION EVALUATION PARAMETERS

Tablet 6: Pre-compression evaluation parameters

Formulation batch	Bulk density(gm/cm^3)	Tapped density(gm/cm^3)	Carre's index%	Hausner's ratio	Angle of Repose θ
F1	0.491	0.593	17.20	1.21	26.32
F2	0.684	0.775	11.74	1.13	27.21
F3	0.857	0.948	9.59	1.10	26.43
F4	0.418	0.494	15.38	1.18	24.81
F5	0.622	0.710	12.39	1.14	25.23
F6	0.709	0.788	10.02	1.11	27.12
F7	1.072	1.181	9.23	1.10	24.42
F8	0.561	0.671	16.39	1.19	25.34
F9	0.465	0.542	14.20	1.16	28.21

POST-COMPRESSION EVALUATION PARAMETERS

Table 7: Post-compression evaluation parameters

Formulation batch	Weight variation (±S.D)	Hardness (Kg/cm3) (±S.D)	Friability (±S.D)%	Wetting time(sec) (±S.D)	Disintegration Time(sec) (±S.D)
F1	498.16±1.07	2.71±0.25	0.44±0.035	20.14±0.50	12.37±1.03
F2	501.05±1.2	2.90±0.31	0.52±0.048	19.35±0.71	11.59±2.02
F3	502.75±1.33	2.85±0.54	0.63±0.055	23.82±0.58	15.26±3.51

F4	503.14±1.21	3.12±0.36	0.46±0.061	21.46±0.76	13.66±0.86
F5	501.78±1.6	2.89±0.58	0.51±0.082	18.88±0.85	10.15±1.06
F6	503.04±1.2	2.67±0.48	0.62±0.064	22.39±0.67	14.84±1.36
F7	498.81±1.2	3.05±0.52	0.71±0.096	25.62±0.35	16.77±2.14
F8	502.98±1.4	3.15±0.21	0.63±0.058	22.17±0.59	13.24±1.15
F9	503.93±1.35	2.92±0.49	0.83±0.091	23.84±0.37	14.31±2.03

Table 8: Post-compression evaluation parameters

Formulation batch	Thickness (mm)(±S.D)	Water Absorption %(±S.D)	In-vitro dispersion time (Sec)(±S.D)	% Drug Content (±S.D)	Fineness of Dispersion
F1	4.21±0.033	49.32±1.56	25.22±1.16	98.36±1.45	Pass
F2	4.28±0.025	43.78±1.96	24.45±1.28	98.49±1.02	Pass
F3	4.25±0.017	53.67±1.04	28.29±1.08	100.97±0.95	Pass
F4	4.23±0.014	63.23±2.74	26.69±1.52	99.03±1.78	Pass
F5	4.27±0.038	72.61±2.14	23.41±2.01	99.59±0.46	Pass
F6	4.22±0.021	57.46±1.78	27.94±1.33	101.43±0.98	Pass
F7	4.24±0.019	59.97±1.45	30.28±2.15	98.62±0.83	Pass
F8	4.26±0.023	61.58±2.38	29.24±1.36	99.76±1.12	Pass
F9	4.25±0.026	48.86±2.71	26.75±1.27	99.29±1.67	Pass

IN-VITRO DISSOLUTION STUDY

The data for in-vitro drug release are shown in Table 9 and dissolution profiles are shown in Figure 2. The in-vitro dissolution study of all nine batches revealed that more than 84% drug release within 10 minute. The maximum dissolution was observed in batch F9 (99.87% drug release within 10 min.). It can be inferred from theresults that batch containing higher concentration of cross povidone and cross carmalose sodium exhibited higher dissolution.

Table 9: Data of % drug release

Time	F1 (±S.D)	F2 (±S.D)	F3 (±S.D)	F4 (±S.D)	F5 (±S.D)	F6 (±S.D)	F7 (±S.D)	F8 (±S.D)	F9 (±S.D)
2	38.51 ±1.02	45.51±1.25	49.02 ±1.24	41.31 ±1.36	45.51 ±2.34	49.35± 1.64	46.27 ±1.47	51.76±1. 06	55.99 ±1.41
4	52.28 ±1.21	55.85±1.08	57.67 ±0.82	56.16 ±1.15	59.35 ±1.26	61.97± 1.71	62.15 ±2.21	64.31±1. 21	68.78 ±1.83
6	66.75 ±1.18	68.43±2.16	69.71 ±1.57	69.96 ±2.19	71.96 ±2.35	73.59± 2.07	77.01 ±2.54	79.37±0. 54	80.86 ±1.69
8	73.71 ±2.13	76.09±2.23	77.91 ±2.13	79.39 ±0.63	81.54 ±1.62	83.34± 1.29	85.55 ±1.35	87.15±1. 76	89.83 ±2.16
10	84.63 ±1.83	85.47±1.34	86.42 ±1.27	91.77 ±1.27	93.28 ±1.76	92.78± 1.65	95.54 ±1.39	97.02±1. 49	99.87 ±1.72

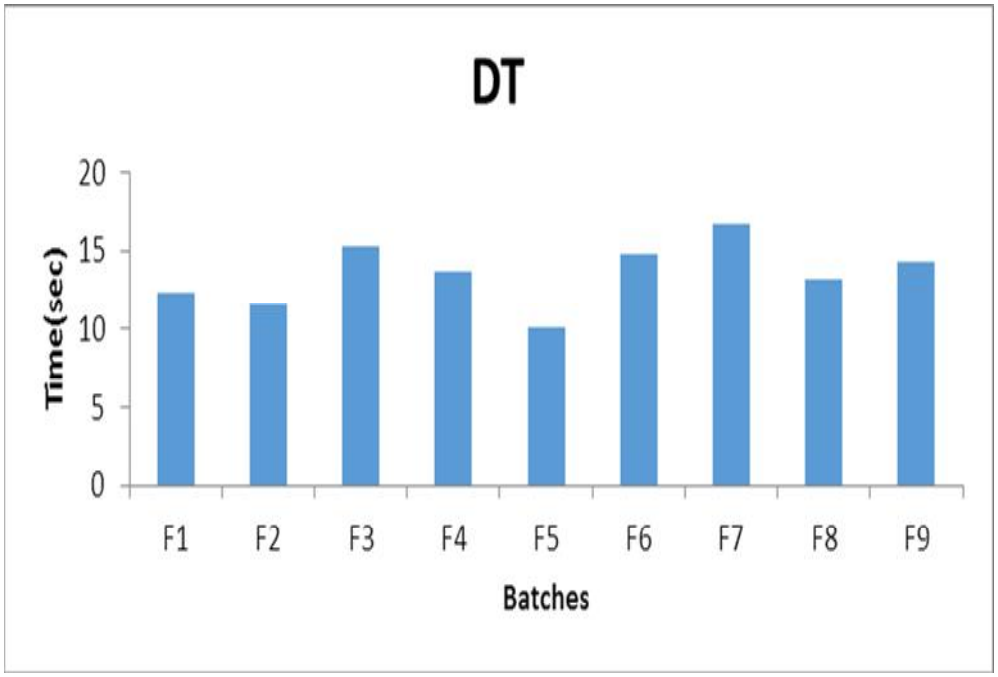

Figure 1: Data of disintegration time

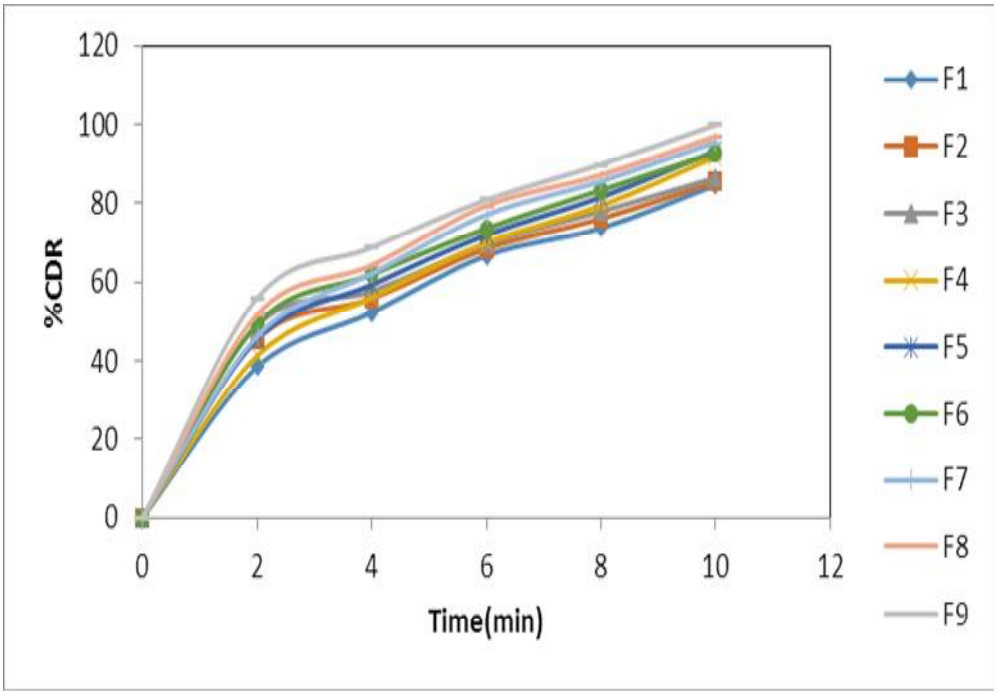

Figure 2: Data of % drug release

FACTORIAL DESIGN

The statistical approach for the optimization is a useful tool, particularly when two variables are to be evaluated simultaneously. A polynomial equation can be generated in case of factorial design, where the coefficients in the equation are related to the effect and interaction of the factor. If the multiple regression coefficients R^2 is nearer to 1, indicates good fit. All

the nine batches were evaluated and different polynomial equations were derived for disintegration time and % drug release in 10 minutes. Results of dependent variables are shown in Table 10.

Table 10: Result of dependent variables of factorial batches

Batch Code	Transformed Value		DT(sec)	%CDR
	X_1^*	X_2^*		
F1	-1	-1	12.37±1.03	84.63±1.83
F2	0	-1	11.59±2.02	85.47±1.34
F3	+1	-1	15.26±3.51	86.42±1.27
F4	-1	0	13.66±0.86	91.77±1.27
F5	0	0	10.15±1.06	93.28±1.76
F6	+1	0	14.84±1.36	92.78±1.65
F7	-1	+1	16.77±2.14	95.54±1.39
F8	0	+1	13.24±1.15	97.01±1.49
F9	+1	+1	14.31±2.03	99.87±1.72

*X_1=Amount of Cross carmalose sodium and X_2= Amount of Cross povidone

Table 11: Data of multiple regression analysis for disintegration time

(A) Multiple regression analysis for disintegration time

Batch Code	X_1^*	X_2^*	X_1X_2	X^2_1	X^2_2	DT(sec)
F1	-1	-1	+1	+1	+1	12.37±1.03
F2	0	-1	0	0	+1	11.59±2.02
F3	+1	-1	-1	+1	+1	15.26±3.51
F4	-1	0	0	+1	0	13.66±0.86
F5	0	0	0	0	0	10.15±1.06
F6	+1	0	0	+1	0	14.84±1.36
F7	-1	+1	-1	+1	+1	16.77±2.14
F8	0	+1	0	0	+1	13.24±1.15
F9	+1	+1	+1	+1	+1	14.31±2.03

* X_1= Cros carmalose sodium X_2= Crospovidone

Observation

Regression equation: $Y= 10.56+0.33X_1+0.83X_2-1.25X_1X_2+2.67X_1^2+1.17X_2^2$

Coefficient (b_0): 10.56

Standard error: 0.54

No. of observation: 9

Correlation coefficient: 0.9702

Table 12: Data of p value and reduced model

	b1	b2	b3	b4	b5
X Coefficient	0.33	0.83	1.25	2.67	1.17
P Value	0.2249	0.0318	0.0186	0.0059	0.0542
Reduce model equation	$Y=10.56+0.83X_2-1.25X_1X_2+2.67X_1^2$				

ANOVA

Table 13: Data of ANOVA

	DF	SS	MS	F	Significance F
Regression	5	28.03	5.61	19.53	0.0170
Residual	3	0.86	0.29		
Total	8	28.89			

DF= degree of freedom SS= sum of square MS= mean sum of square F=fischer's ratio

To identify the important parameters affecting the disintegration time, the stepwise multiple regression data was analyzed.

$$Y= 10.56+0.33X_1+0.83X_2-1.25X_1X_2+2.67\ X_1^2+1.17\ X_2^2 \text{ (Full model)}$$

The value of R^2 obtained was 0.9702, which indicate good fit. It can be seen from the finding that X_2, $X_1X_2$and X_1^2 factors had significant effect on DT with P value < 0.05.While X_2^2 and X_1 were non-significant (P > 0.05). Therefore, the reduced model equation is:

$$Y=10.56+0.83X_2-1.25X_1X_2+2.67X_1^2$$

It was observed that, the coefficients of X_1 and X_2 showed positive effect, which indicated that as the values of X_1 and X_2 were increased, the response was also increased it means that as the amount of CCC and CRP increased, the DT of the tablets were increased. The effects of the X_1 and X_2 on the response are also studied graphically from Figure 3 and 4 respectively. At medium level of X_1 and X_2, the DT was decreased and as the levels of X_1 and X_2 were increased, the response was increased. The blue color zone in the both mentioned plots show the lower DT at different combination of X_1 and X_2factor.

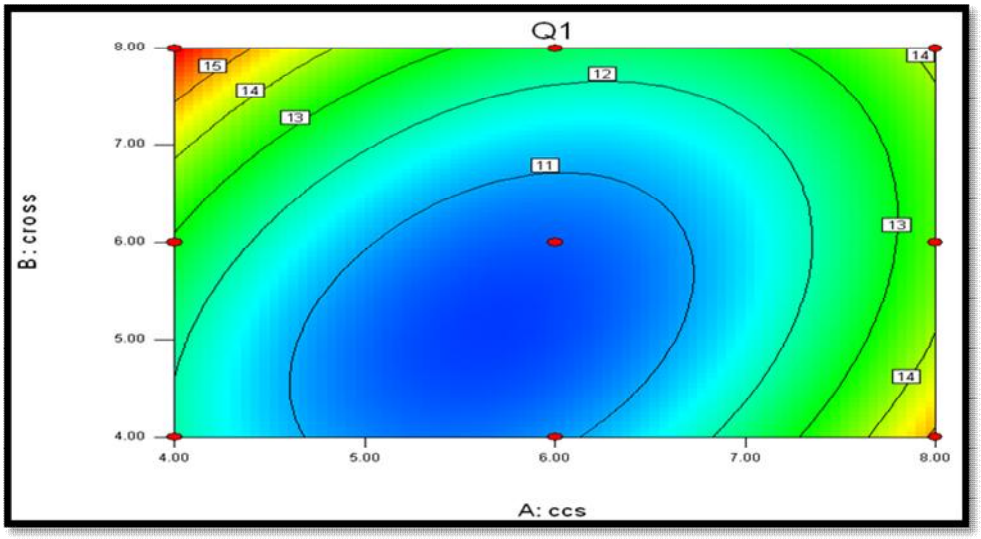

Figure 3: Contour plot for disintegration time

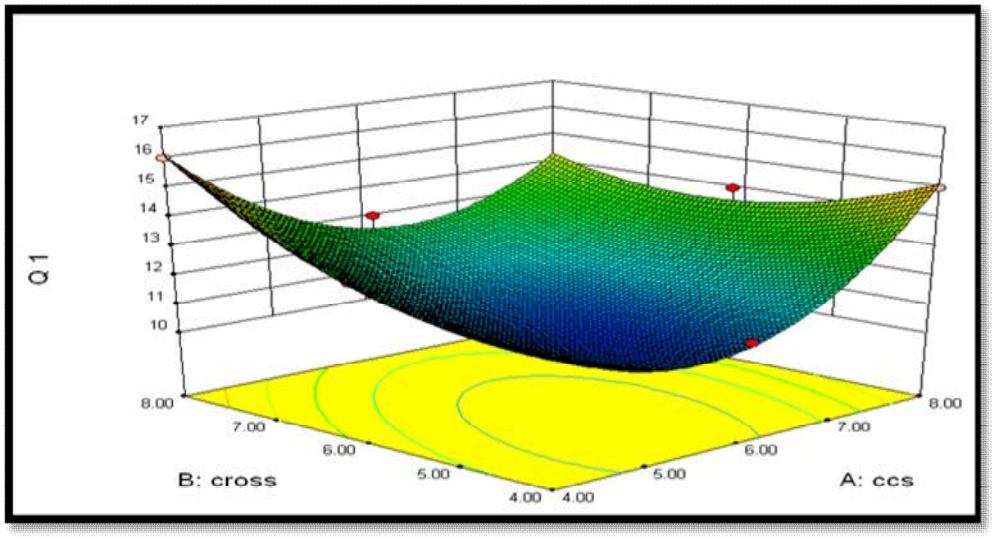

Figure 4: Response surface plot for disintegration time

Table 14: Data of multiple regression analysis for %drug release in 10min

(B)Multiple regression analysis for %drug release in 10min

Batch Code	X_1	X_2	X_1X_2	X^2_1	X^2_2	%CDR
F1	-1	-1	+1	+1	+1	84.63±1.83
F2	0	-1	0	0	+1	85.47±1.34
F3	+1	-1	-1	+1	+1	86.42±1.27
F4	-1	0	0	+1	0	91.77±1.27
F5	0	0	0	0	0	93.28±1.76
F6	+1	0	0	+1	0	92.78±1.65
F7	-1	+1	-1	+1	+1	95.54±1.39
F8	0	+1	0	0	+1	97.01±1.49
F9	+1	+1	+1	+1	+1	99.87±1.72

* X_1= Cros carmalose sodium X_2= Crospovidone

Observation

Regression equation: $Y= 91.86+1.19X_1+5.98X_2$

Coefficient (b_0): 91.86

Standard error: 1.04

No. of observation: 9

Correlation coefficient: 0.9716

Table 15: Data of p value and reduced model

	b1	b2
X Coefficient	1.19	5.98
P Value	0.0313	0.0001
Reduce model equation	$Y=91.86+1.19X_1+5.98X_2$	

ANOVA

Table 16: Data of ANOVA

	DF	SS	MS	F	Significance F
Regression	2	223.42	111.71	102.78	0.0001
Residual	6	6.52	214.92		
Total	8	229.94			

DF= degree of freedom SS= sum of square MS= mean sum of square F= fischer's ratio

To identify the important parameters affecting the %drug release, the stepwise multiple regression data was analyzed.

$$Y= 91.86+1.19X_1+5.98X_2 \text{ (Full model)}$$

The value of R^2 obtained was 0.9716, which indicate good fit. It can be seen from the finding that X_1, X_2 factors had significant effect on %drug release with P value < 0.05.Therefore, the reduced model equation is:

$$Y=91.86+1.19X_1+5.98X_2$$

It was observed that, the coefficients of X_1 and X_2 showed positive effect, which indicated that as the values of X_1 and X_2 were increased, the response was also increased it means that as the amount of CCC and CRP increased, the %drug release of the tablets were increased. The effects of the X_1 and X_2 on the response are also studied graphically from Figure 5 and 6 respectively. At medium level of X_1 and X_2, the %drug release was decreased and as the levels of X_1 and X_2 were decreased, the response was decreased.

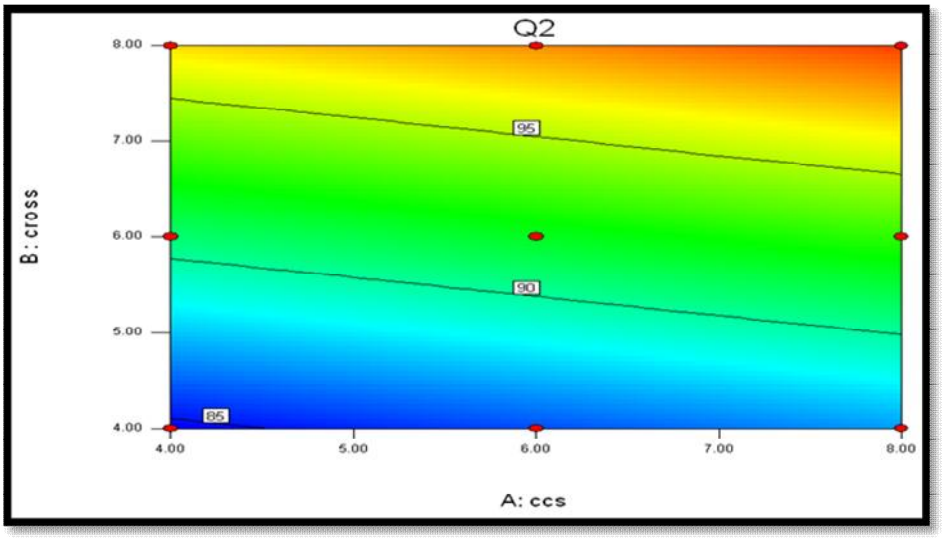

Figure 5: Contour plot for %drug release in 10min

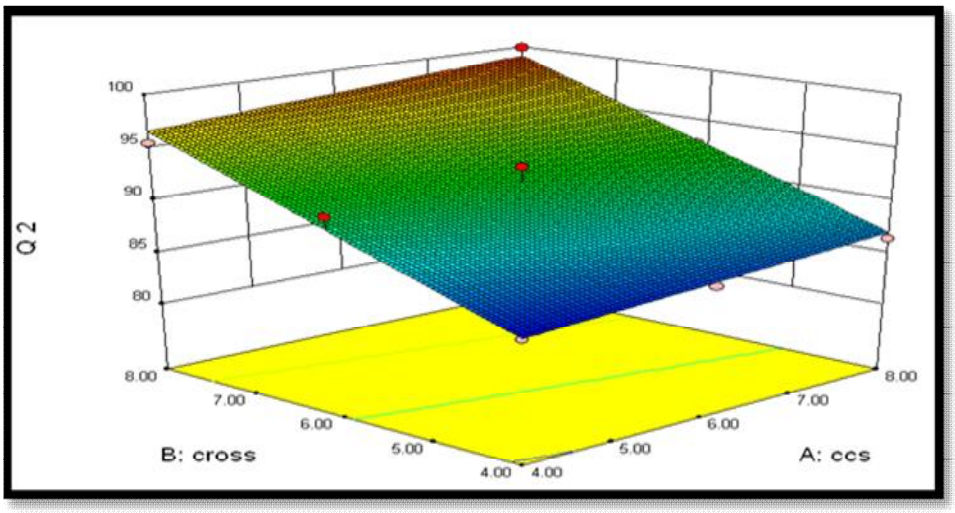

Figure 6: Response surface plot for %drug release in 10min

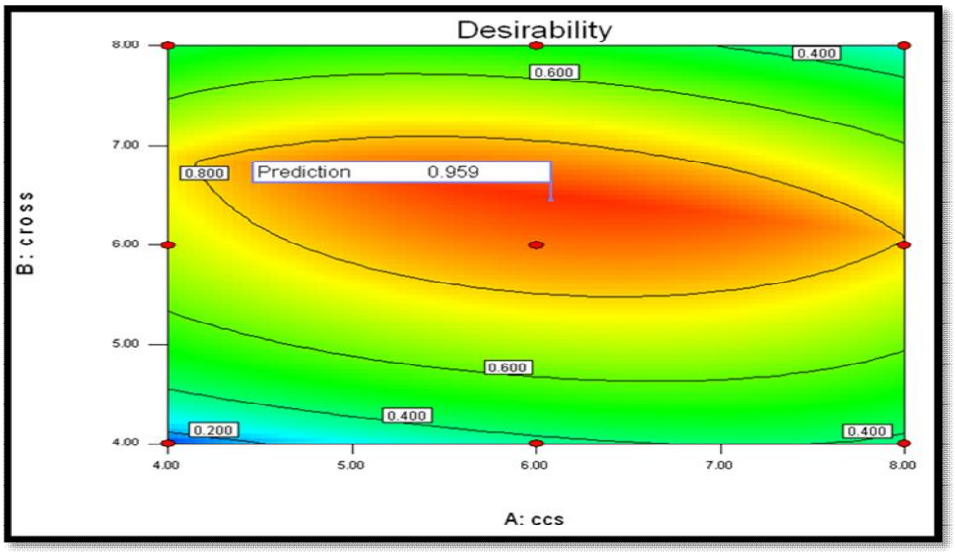

Figure 7: Desirability plot

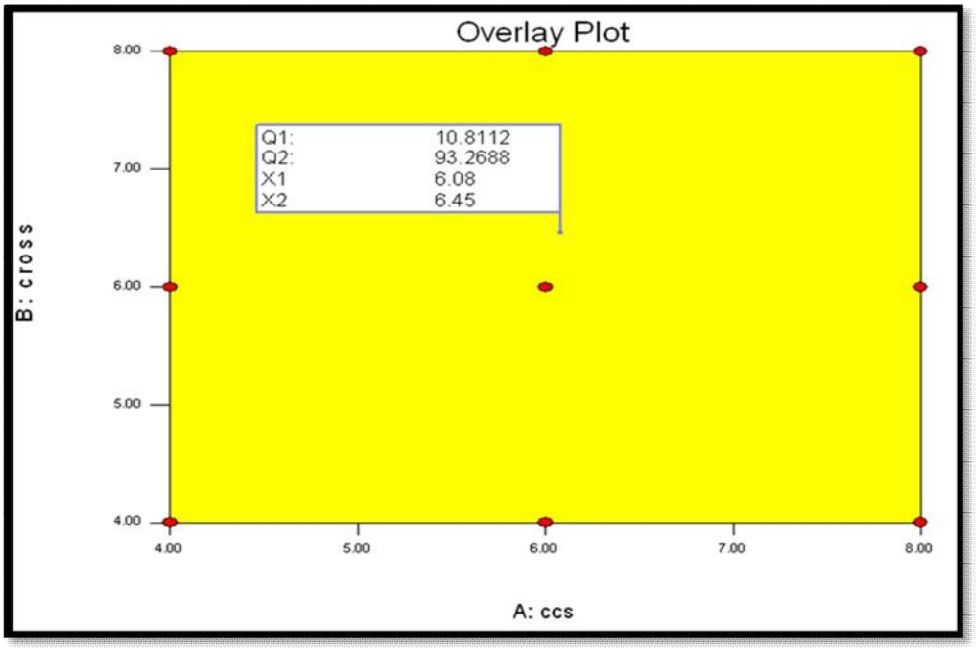

Figure 8: Overlay plot

BATCH OPTIMIZATION

The desirability study showed that the prediction0.959 when 6% cross carmalose sodium and 6% cross povidone are used. The overlay plot reflects that **Batch F5** 6.08% cross carmalose sodium and 6.45% cross povidone is selected as optimized batch based on prediction value.

STABILITY STUDIES

Results of stability study are shown in Table 17.

Table 17: Results of stability studies of F5 batches of ODTs Initial and after 1month stability chamber

Parameters	Initial	After 1 month
Disintegration time(sec)	10.15±1.06	11.52±1.23
Drug content (%)	99.59±0.46	98.34±0.67

The results of stability studies revealed that there was no remarkable difference in the tested parameters of optimizing batches after storage for 1 month as compared to initial results. The results of stability study demonstrated that the selected formulations were found to be stable**.**

CONCLUSION

Attempt was made in the present investigation to formulate an oro-dispersible tablet of Metformin Hcl by using direct compression method. Formulation was carried out using different super disintegrants and the concentration of the disintegranting agent was optimized

to give minimum disintegration time and maximum drug release. Preliminary 9 trial batches were formulated by using three super disintegrants i.e. sodium starch glycolate, cross carmellose sodium and cross povidone. The batches were evaluated for disintegration time, wetting time and hardness. Based on the evaluated result, two super disintegrants like cross carmelose sodium and cross povidone were selected; were further formulated study on the bases of the effect of the different concentration of super disintegrants. A 3^2 full factorial design was employed for preparation of tablets possessing optimized characteristics (Batch F1-F9). The amount of CCS (X_1) and CRP (X_2) were selected as independent variables. Disintegration time and % CDR at 10 min were selected as dependent variable. Full and reduced models were derived for the prediction of the response variable, Y. Based on result of multiple linear regression analysis, it was concluded that lower disintegration time and acceptable % CDR of tablets could be obtained when X_1 and X_2 at optimum level is concentration 6%. Tablets of batch F5 exhibited better drug dissolution after 10 min. The stability study of developed tablet formulation was carried out in stability chamber at 40± 2.0˚C and 75±5% RH for 1 month. The tablets were stable at this condition (Stability temp at 40± 2.0˚C and 75±5% RH) for a period of one month without any significant change in vitro drug release.

REFERENCES

1. Diabetes fact sheet, who, November 2008.
2. Bastaki S, Diabetes mellitus and its treatment, “Intrenational Journal Diabetes & Metabolism”, 2005; 13: 111-134.
3. Harkrishan S, Kapoor VK, Medicinal and pharmaceutical, 2nd edition, 377, 2005.
4. Chien YW, “Novel drug delivery systems”, New york – marcel dekker inc., 2nd edition 1992.
5. Sameer G, Late, Yi-yingyu, Ajay k, “Effect of disintegration- promoting agent, lubricants and moisture treatment on optimized fast disintegrating agent”, International Journal of Pharmaceutical Sciences and Research, 2008; 1-8.
6. Bandari S, Mittapalli RK, Gannu R, Rao MY, “orodispersible tablets: An overview. Asian J Pharm”, 2008; 2-1.
7. Sharma D, Kumar D, Sing M, Sing G, Rathor M.S, “Fast disintegrating tablets: A New Era In Novel Drug Delivery System And New Market Opportunities”, Journal of Drug Delivery & Therapeutics,2012; 2(3): 74-86.

8. Debjit B, Chiranjib B, Krishnakanth, Pankaj, Margret R, Chandira, "Fast dissolving tablet: An Overview", Journal of Chemical and Pharmaceutical Research, 1(1), 2009.
9. Nandy B, Mazumder B, Pathak K, Saxena N, Jain S, Sharma S, Amishaben R, Shrivastava A, Saxena P, "An Overview on fast dissolving drug delivery system", Asian Journal Of Pharmaceutical Sciences And Research, 1(2), 2011.
10. Sreenivas SA, Dandgi PM, Gadad AP, Godbpersible AM, Hiremath SP, Bhagavati ST, "Orodispersible tablets: New-fangled drug delivery system", Indian Journal of Pharmaceutical Education and Research, 2005; 39(5):177-181.
11. Gupta A, Mittal A, Jha K, "Fast dissolving tablet – A Review", The Pharma innovation, 1(1); 2012.
12. Swamivelmanickam M, Manavalan R, Valliappan K, "Mouth dissolving tablets: An Overview", International Journal of Pharmaceutical Sciences and Research,2010; 1 (12): 43-55.
13. Yourong F, Yang S, Jeong S, Kimura S, Park K, "Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies", Critical Reviews™ in Therapeutic Drug Carrier Systems, 2004; 21(6): 433–475.
14. Ankita P, M.pharm Thesis, "Formulation development and optimization of floating matrix tablet of Atenolol", Gujarat Technological University, June, 2011.
15. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=86d268f3-994c-4678-1e14-8021083cc490
16. http://www.drugbank.ca/drugs/DB00331
17. Indian Pharmacopoeia, Ministry of Health & welfare, Ghaziabad, India, Pharmacopoeial commission, 2010; 2: 1657.
18. http://en.wikipedia.org/wiki/Metformin.
19. Rowe RC, Sheskey PJ, Owen SC, 5thHandbook of pharmaceutical excipients, pharmaceutical press, 132; 2006.
20. Rowe RC, Sheskey PJ, Owen SC, 5thHandbook of pharmaceutical excipients, pharmaceutical press, 214; 2006.
21. Rowe RC, Sheskey PJ, Owen SC, 5thHandbook of pharmaceutical excipients, pharmaceutical press, 211; 2006.
22. Rowe RC, Sheskey PJ, Owen SC, 5thHandbook of pharmaceutical excipients, pharmaceutical press, 430; 2006.
23. Rowe RC, Sheskey PJ, Owen SC, 5thHandbook of pharmaceutical excipients, pharmaceutical press, 449; 2006.

24. Rowe RC, Sheskey PJ, Owen SC, 5thHandbook of pharmaceutical excipients, pharmaceutical press, 767; 2006.
25. Readdy AM, Siddika A, Rao PSB, Manasa P, Siddaiah J, Babu PS, "Formulation and evaluation of sustained release matrix tablets of metformin hydrhocloride", Indian journal of research in Pharmacy and Biotechnology, 2013; 1(2):197-200.
26. Rajesh M, Pippalla M, Krsc b, Sundaram M.S, Palanichamy S, Thirupathi AT," Formulation and evaluation of extended release tablets of metformin hydrochloride", International journal of pharmaceutical, chemical and biological sciences, 2012; 2(3): 318-324.
27. Mura P, Corti g, Cirri M, Maestrelli F, Mennini N, "Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-b-cyclodextrin",European journal of pharmaceutics and biopharmaceutics, 2008; 303–309.
28. Hajare AA, Patil VA, "Formulation and characterization of metformin hydrochloride floating tablets", Asian journal pharmaceutical and clinical research, 2012; 2(3): 111-117.
29. Cheng C, Yu L, Lee H, Yang C, Lue C, Chou C, "Biowaiver extension potential to BCS Class III high solubility-low permeability drugs: bridging evidence for metformin immediate-release tablet", European Journal of Pharmaceutical Sciences, 2004;297-302.
30. Hu L, Liu Y, Tang X, Zhang Q, "Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets", European Journal of Pharmaceutics and Biopharmaceutics, 2006;185-192.
31. Mathew F, Anoop KR, Jose S, Jose A, "Formulation of metformin hydrochloride matrix tablets by sintering technique and its evaluation", International journal of pharmacy & technology, 2010; 2(2): 293-306.
32. kumar R, Chandra A, Garg S, "Formulation and in vitro evaluation of sustained release gastro retentive tablets of metformin hydrochloride", International Journal of Therapeutic Applications,2012; 7: 13-17.
33. Ramana BV, Spandana DC, Triveni C, Kumar V, Reddy V, Chandra U, "Comparative in vitro drug release studies of glimepiride solid dispersions & metformin microcapsules", International Journal of Pharmaceutical Sciences and Research", 2013; 4(11): 4329-4335.
34. Metkari VB, Kulkarni LV, Patil PS, Jadhav PA, Jadhav PH, Yadav PS, "Formulation and evaluation of orodispersible tablet of theophylline using different super disintegrants", International journal of pharmacy research, 2014; 02(1): 47-59.
35. Schiermeier S, Schmidt PC, "Fast dispersible ibuprofen tablets", European Journal of Pharmaceutical Sciences, 2002; 15: 295-305.

36. Huda G, Toshniwal SS, "Formulation taste masked orodispersible tablet of Pregabalin", International Journal of Drug Delivery, 2013; 56-62.
37. Jadhav Y, Bharat P, "Formulation and evaluation of mouth dissolving tablet of glipizide by solid dispersion", International journal of pharmaceutical sciences and research, 2012; 3(12): 4929-4937.
38. Rawat P, Mote P, Singh S, Salunke A, Rajendra V, Zadbuke N, "Fast dissolving tablets of pioglitazone hydrochloride by use of various superdisintegrants", International journal of advanced research in pharmaceutical & bio-sciences, 2013; 3(2): 74-79.
39. Swamy K, Narender D, Goud A, "Formulation and evaluation of orodispersible tablet of theophylline using different super disintegrants", Journal of advanced pharmaceutical sciences, 2012 2(2): 260-266.
40. Mizumoto T, Masuda Y, Yamamoto T, Yonemochi E, Terada K, "Formulation design of a novel fast-disintegrating tablet", International Journal of Pharmaceutics, 2005;83-90.
41. Velmurugan S, Vinushitha S, "Oral Disintegrating Tablets: An Overview", International Journal of Chemical and Pharmaceutical Sciences, 1(2), 2010.
42. Maan S, Jogpal V, "Fast disintegrating tablets: Opportunity in drug delivery system", Journal of Advanced Pharmaceutical Technology & Research.
43. Solanki S, Dahima R, "Formulation and evalution of aceclofenac mouth dissolving tablet", Journal of advanced Pharmaceutical Technology & Research.
44. Jyothi P, "Mouth dissolving tablets- review", International journal of advances in pharmacy, biology and chemistry, 2012; 1(4): 477-484.
45. Patwa S, Narang N, Singla R, An Overview On Fast Dissolving.