IJPSR (2018), Volume 9, Issue 10 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 January, 2018; received in revised form, 12 September, 2018; accepted, 17 September, 2018; published 01 October, 2018

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF METFORMIN HYDROCHLORIDE USING AGAR AS NATURAL SUPER DISINTEGRANT

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Keywords:

Metformin HCl, Orodispersible tablets, Treated Aaar, Diabetes mellitus, Drug delivery system, Immediate release

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ABSTRACT: The objective of the present work is to develop orodispersible tablets of Metformin hydrochloride using agar as natural super disintegrant to improve bioavailability, disintegration time, dissolution efficacy and patient compliance. Fast dissolving drug delivery system has numerous advantages over conventional dosage form like tablet, capsule, syrups *etc*. Formulation of nine batches out of which batch F5 with 6% super disintegrant was found to have better results in compare to other formulations, the F5 batch was passed with friability test and found negligible loss (0.4%), Then the batch was further evaluated for disintegration test and found to have 11.03 sec and *in-vitro* dispersion was found to be 15 sec in simulated saliva fluid and percentage drug release was evaluated to be 98.5% in less than 30 min. Hence, F5 batch was found to be better as it contain 6% treated agar. It shows further potential to carry animal model.

INTRODUCTION: Diabetes is a metabolic disorder marked by higher levels of sugar in blood as a result of defects in insulin secretion, action of insulin or both [1]. Surveys by authentic and prominent bodies throughout the world have had estimated a step rise in the number of diabetic cases throughout, with cases in almost every continent of the world, diabetes has now becoming a pandemic. It has been estimated that by 2030 about 438 million people of the adult population would be suffering from diabetes with the highest share from that of the developing economies including India and China [2]. The global prevalence of diabetes is due to various factors like population growth, aging, urbanization and obesity.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(10).4220-28

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(10).4220-28

The main determining factor of the pandemic is fast epidemiological transition related to change in the food habits and lesser physical activity. While the western part of the world sees a rise in the number of diabetes belonging to the old age groups; Asian population shows a reverse trend where the number of diabetes cases are disproportionality higher in younger to middle age group population [3].

This trend of diabetes can have a long term negative impact to nation's health economy especially for developing countries. Healthcare expenditure on diabetes is expected to raise higher and higher taking a major chunk of the total expenditure. By 2030 global healthcare spending in the management of diabetes is expected to touch a whopping USD 500 billion [4]. While medical science has developed to an extent par-imagination, a permanent cure for the disorder still remains a quest. Various moieties including biguanides, glitazones, sulfonylureas and α – glucosidase inhibitors have been developed as a treatment for diabetes at times insulin obtained

from bovine / procaine sources or synthetically derived is also administered the research still continues with development of newer alternatives (like gliptins). These moieties do offer a promising treatment to store the normal glycemic levels in the body, at some points or the other; they also suffer major disadvantages as they may lead to certain side effects. Analyzing the risk to benefit ratio and the suitability Metformin hydrochloride (Metformin / MHCl), a prominent member of the biguanide classes is generally chosen as a first line of treatment for diabetes since adverse events linked to Metformin (gastrointestinal disturbances most prominently) do fade off on repeated usage however fatal events as lactic acidosis though can't be ruled out but the chances of happening as such is very bleak. It can rightly said, Metformin is one of the best alternative available today for controlling of diabetes [5].

MATERIALS AND METHODS:

Materials: Metformin hydrochloride was obtained as a gift sample from Tanpal Pharmacy, Chandigarh of pharmaceutical grade, Agar was obtained from Fisher Scientific of microbiological / pharmaceutical grade, avicel - 101 was obtained from FMC Biopolymer of pharmaceutical grade, talc was obtained from Lobachemie Pvt. Ltd., of pharmaceutical grade extra pure; batch no. D031306, magnesium stearate was obtained from Central Drug House Pvt. Ltd., (New Delhi) and mannitol was obtained from Fisher Scientific Qualigens Thermo electron L1s India Pvt. Ltd., (Mumbai) of pharmaceutical grade; product no. 25275; Lot no.6576/1

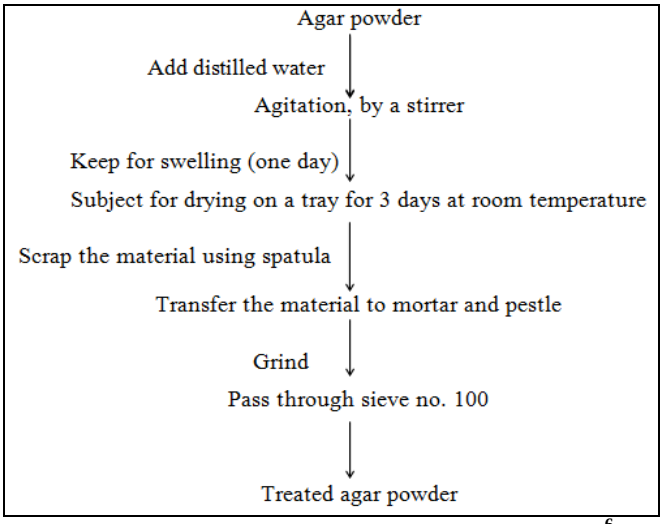

FIG. 1: PREPARATION OF TREATED AGAR [6]

Methods:

Preparation of Super disintegrant: Treated agar was used as a super disintegrant. Suitable quantity of agar powder (5-10 g) weighed and added in distilled water (100 ml). Agitation was done continuously for 1 day by stirrer to swell the contents. The swollen contents were dried for 3 days at room temperature. The dried powder was ground and passed through sieve no. 100. [6]

Pre-formulation Studies: Pre-formulation involves the application of biopharmaceutical principle to the physicochemical parameters of the drug substance are characterized with the goal of designing optimum drug delivery system. The current research and endeavor aims at using super disintegrant of natural origin for the development of the oral dispersible tablets of Metformin by using direct compression.

Physicochemical Properties of Metformin: The various physicochemical properties of Metformin and treated agar includes such as nature [7].

- Color
- Solubility
- Melting point

Drug Excipient Compatibility: Drug excipient compatibility was assured by FT-IR absorption spectra of the drug were obtained, using the potassium bromide (KBr) disk technique [8].

Evaluation of Pre- Compression Parameter:

Bulk Density (D_b): It is the ratio of the total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (pre-sieved 40-mesh) into a measuring cylinder via large funnel and recording the volume and weight "as is. This initial volume is called the bulk volume. From this the density is calculated to the formula [8]:

$$Db = M / V_b$$

Where, M is the mass of powder, V_b is the bulk volume of the powder.

Tapped Density (D_t): The sifted powder of the known mass was then poured into a measuring cylinder and subjected to 100 tapings in a bulk density apparatus and the final tapped volume (V_t) occupied. The values obtained were put into the formula to obtain tapped density [8].

$$D_t = M / V_t$$

Where, M is the mass of powder, V_t is the tapped volume of the powder.

Angle of Repose (e): The powder blend was poured through a wide funnel attached to a stand so as to increase/ decrease the height of the tip of the funnel from the obtained heap of the blend the height (h) of the heap and the radius of the base was then recorded and computed according to the formula: [8]

$$\text{Tan } (\Theta) = h / r \text{ or } \Theta = \tan^{-1} (h / r)$$

Where, Θ is the angle of repose, h is the height of the pile on cm, r is the radius of the pile in cm.

Carr's Index (or) % Compressibility: It indicates powder flow properties. It is expressed in % and is given by: [9]

$$I = D_t - D_b / D_t \times 100$$

Where, D_t is the tapped density, D_b is the bulk density.

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

$$\text{Hausner's ratio} = D_t / D_b$$

Where, D_t is the tapped density, D_b is the bulk density.

Formulation of the Orodispersible Tablets:

Direct Compression Method: The orodispersible tablets were prepared by a direct compression method. The drug mixture was prepared by homogeneously mixing the required quantities of Metformin HCl, avicel- 101, mannitol and treated agar.

All the ingredients of the orodispersible tablets of Metformin HCl was weighed, shifted, then in the last magnesium stearate and talc was added as lubricating agent. The 500 mg mixture was then compressed using a 12 mm punch in a tablet punching machine. Each tablet weighed 500 mg.

Evaluation of ODT's for Quality Parameters: All the prepared tablets were evaluated for the following parameters as per I.P. guidelines:

Weight Variation: 20 tablets were randomly selected from each batch, individually weighed, the average weight and standard deviation of 20 tablets was calculated [10].

Wetting Time: Wetting time is related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the equation proposed by Washburn E.W (1921), the penetration rate of water into the powder bed is directly proportional to the pore radius and depends upon the hydrophilicity of the powders. A piece of tissue paper folded double was placed in petry plate (internal dia. is 6.5 cm) containing 6 ml of water. The tablet was placed on the paper and the time for the complete wetting of the tablet was measured in seconds. The method was modified by maintaining water temperature at 37 °C. A total of 6 tablets from a batch was randomly selected and analyzed for wetting time while the average wetting time recorded [10].

Hardness: Hardness or tablets crushing strength (Fc) is the force required to break a tablet in a diametric compression and was measured using a Monsanto /Pfizer tablet hardness tester [11].

***In-vitro* Dispersion Time:** The tablet was added to 6ml of phosphate buffer solution pH 6.8 at 37 ± 0.5 °C time required for complete dispersion of a tablet was measured. The test was carried out on at least 3 tablets randomly selected from a batch while average readings are recorded [12].

Friability: Friability of tablets was determined using Roche friabilator (USP). Pre weighed sample of tablets or a defined tablets (in this case, 10) was placed in the friabilator and were subjected to 100 revolutions at 25 rpm [13].

$$\% \text{ friability} = [\text{Initial wt.} - \text{Final wt.} / \text{Initial wt.}] \times 100$$

***In-vitro* Disintegration Time:** The disintegration test was performed using disintegration apparatus (USP device) with distilled water at 37 ± 0.5 °C. Effect of super disintegrants was studied. The test was carried on 6 tablets selected randomly from a batch and average value recorded [14].

Dissolution Test: Dissolution rate of Metformin HCl from all the formulation was performed using USP type 2 dissolution apparatus. The dissolution

fluid was 900 ml of 6.8 pH phosphate buffer at a speed 50 rpm and temperature of 37 ± 0.5 ℃. Samples of dissolution medium (5 ml) were withdrawn at regular intervals of 5 min till 30 min. The absorbance of Metformin HCl was measured at 233 nm by UV. The dissolution parameters and correlation coefficient values were calculated [15].

Drug Content Uniformity: The drug content was determined by taking the powder equivalent to 10mg of Metformin HCl, then it was extracted in phosphate buffer 6.8 pH (100 ml) concentration of drug was determined by measuring absorbance at 233 nm by UV [16].

TABLE 1: FORMULATION OF METFORMIN ODT (IN PERCENTAGE)

S. no.	Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Metformin	50	50	50	50	50	50	50	50	50
2	Treated agar	2	3	4	5	6	7	8	9	10
3	Avicel-101	36	35	34	33	32	31	30	29	28
4	Magnesium stearate	1	1	1	1	1	1	1	1	1
5	Talc	1	1	1	1	1	1	1	1	1
6	Mannitol	10	10	10	10	10	10	10	10	10

RESULTS:

Physiochemical Properties of Metformin HCl:

- Color: White (Crystalline)
- Solubility: Soluble in water and 95% ethanol
- Melting Point: 217-222 ºC.

Compatibility of Metformin:

Infrared Spectroscopy Study: No change in the shape of peak or shift of the peak ensured the compatibility of the excipients.

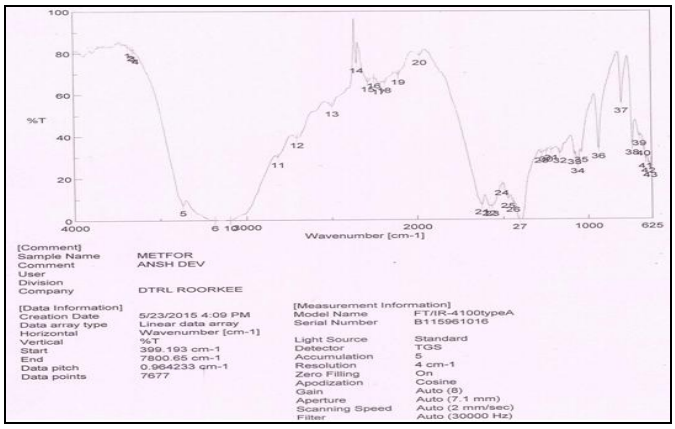

FIG. 2: IR SPECTRA OF METFORMIN HCl

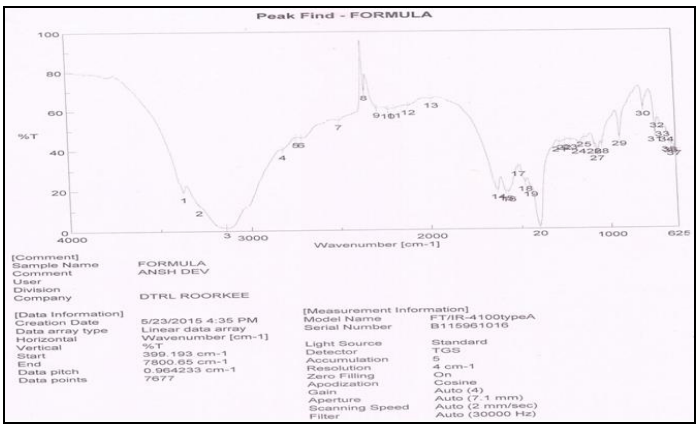

FIG. 3: IR SPECTRA OF BLEND

UV Spectroscopy: The Lambda Max for Metformin solution in distilled water was found to be 233 nm.

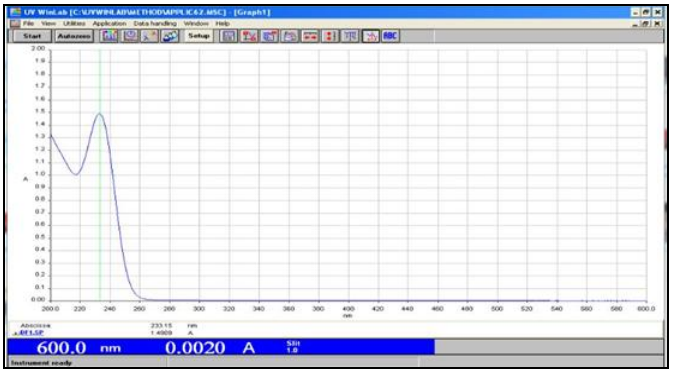

FIG. 4: UV SPECTRA OF METFORMIN HCl DETERMINING LAMBDA MAX

Evaluation of Pre- Compression Parameters:

Bulk Density:

TABLE 2: BULK DENSITY

Batches	Mass (g)	Volume (cm^3)	Bulk density (gm. / cm^3)
F1	5	9.2	0.54
F2	5	9.2	0.54
F3	5	9.0	0.55
F4	5	9.0	0.55
F5	5	9.0	0.55
F6	5	9.0	0.55
F7	5	9.2	0.54
F8	5	9.2	0.54
F9	5	9.2	0.54

Tapped Density:

TABLE 3: TAPPED DENSITY

Batches	Mass (g)	Volume (cm^3)	Tapped density (g/cm^3)
F1	5	7.8	0.64
F2	5	7.8	0.64
F3	5	7.9	0.63
F4	5	7.9	0.63
F5	5	7.9	0.63
F6	5	7.9	0.63
F7	5	7.8	0.64
F8	5	7.8	0.64
F9	5	7.8	0.64

Angle of Repose: Angle of repose was found near the acceptable range (<= 30 degrees) ensuring the free flowing of blend.

TABLE 4: ANGLE OF REPOSE

Batches	Height (cm)	Radius (cm)	Angle of repose (tan Ɵ)
F1	2.6	4.0	33.0
F2	2.5	4.2	30.0
F3	2.5	4.3	30.1
F4	2.7	4.3	31.7
F5	2.7	4.2	32.6
F6	2.6	4.1	32.2
F7	2.6	4.0	33.0
F8	2.5	4.3	30.1
F9	2.5	4.3	30.1

Compressibility of Index: The % compressibility of F1, F2, F7, F8, F9 indicated excellent flowability (5-15%) while F3, F4, F5 F6 showed good flowability (12-16%)

TABLE 5: COMPRESSIBILITY OF INDEX

Batches	Tapped density (g/cm^3)	Bulk density (g/cm^3)	% compressibility
F1	0.64	0.54	15.62
F2	0.64	0.54	15.62
F3	0.63	0.55	12.69
F4	0.63	0.55	12.69
F5	0.63	0.55	12.69
F6	0.63	0.55	12.69
F7	0.64	0.54	15.62
F8	0.64	0.54	15.62
F9	0.64	0.54	15.62

Hausner's Ratio: The values of hausner's ratio was calculated were lower hausner's ratio (<1.125) indicated better flow properties.

Evaluation of ODTs:

Weight Variation: The weight variation test was carried out by weighing each 20 tablets, then calculating the avg. weight and comparing the individual tablet weight to the average. Acceptance: No more than 2 tablets should be outside the percentage limit to pass the test and if more than 2 tablets are found outside the range percentage limit they fail. The formed tablets pass the weight variation test.

TABLE 6: HAUSNER'S RATIO

Batches	Tapped density (g/cm^3)	Bulk density (g/cm^3)	Hausner's ratio
F1	0.64	0.54	1.185
F2	0.64	0.54	1.185
F3	0.63	0.55	1.145
F4	0.63	0.55	1.145
F5	0.63	0.55	1.145
F6	0.63	0.55	1.145
F7	0.64	0.54	1.185
F8	0.64	0.54	1.185
F9	0.64	0.54	1.185

Wetting Time:

TABLE 7: WETTING TIME

Batch	Wetting time
F1	51.67
F2	48.32
F3	36.77
F4	29.93
F5	26.66
F6	26.60
F7	23.11
F8	20.70
F9	12.43

Hardness:

TABLE 8: HARDNESS

Batch	Hardness (±SD)
F1	4 ± 0.33
F2	4 ± 0.32
F3	3 ± 0.24
F4	4 ± 0.25
F5	4 ± 0.23
F6	3 ± 0.34
F7	2 ± 0.29
F8	2 ± 0.12
F9	2 ± 0.15

In-vitro Dispersion Time:

TABLE 9: *IN-VITRO* DISPERSION TIME

Batch	*In-vitro* dispersion time(in sec)
F1	49.86
F2	46.33
F3	45.90
F4	43.29
F5	15.60
F6	15.43
F7	11.22
F8	9.08
F9	6.20

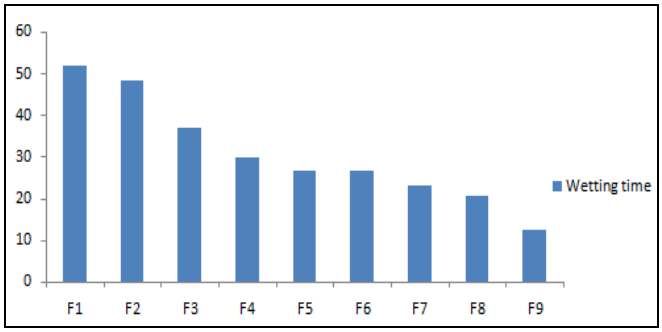

FIG. 5: WETTING TIME

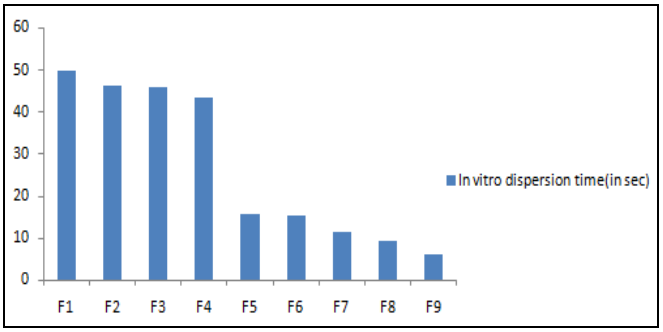

FIG. 6: *IN- VITRO* DISPERSION TIME (IN SEC)

Disintegration Time:

TABLE 10: DISINTEGRATION TIME (IN SEC)

Batch	Disintegration time (in sec)
F1	15.71
F2	15.02
F3	13.90
F4	12.58
F5	11.03
F6	11.13
F7	10.01
F8	9.02
F9	7.25

Friability:

TABLE 11: FRIABILITY

Batch	Initial weight (g)	Final weight (g)	% Friability [Initial wt. – final wt. / initial wt.] × 100
F1	5	4.99	0.2
F2	5	4.97	0.6
F3	5	4.99	0.2
F4	5	4.98	0.4
F5	5	4.98	0.4
F6	5	4.90	2
F7	5	4.92	1.6
F8	5	4.95	1
F9	5	4.96	0.8

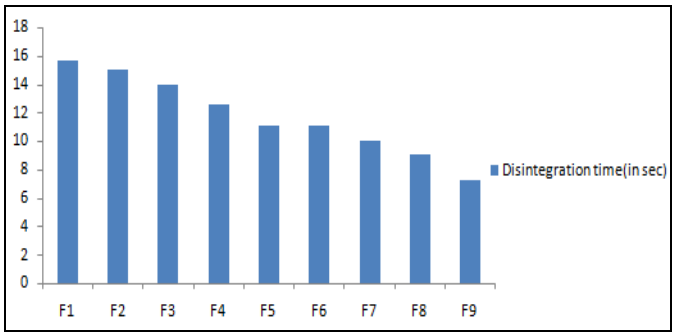

FIG. 7: DISINTEGRATION TIME (IN SEC)

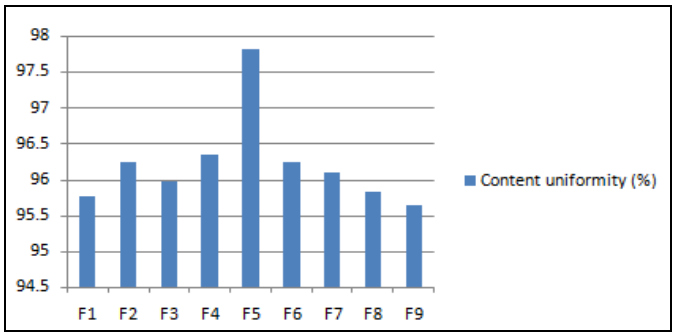

FIG. 8: CONTENT UNIFORMITY (%)

Drug Content Uniformity:

TABLE 12: DRUG CONTENT UNIFORMITY

Batch	Content uniformity (%)
F1	95.76
F2	96.25
F3	95.98

F4	96.34
F5	97.82
F6	96.24
F7	96.1
F8	95.82
F9	95.63

Dissolution: Calibration curve of Metformin HCl using UV spectroscopy.

TABLE 13: ABSORBANCE

Concentration (µg/ml)	Absorbance at 233 nm
2	0.1668
3	0.2419
4	0.3181
5	0.4034
6	0.4809
7	0.5505
8	0.6375
9	0.7260
10	0.8070

Cumulative Drug Release:

TABLE 14: CUMULATIVE DRUG RELEASE

Batches	% Cumulative Drug Release					
	5min	10 min	15 min	20 min	25 min	30 min
F1	72.54	74.83	83.92	84.52	89.01	95.33
F2	73.33	75.94	85.58	85.99	90.01	97.02
F3	74.59	77.44	80.59	83.21	92.36	98.37
F4	78.03	79.99	81.11	85.98	94.78	98.45
F5	80.98	86.40	92.01	95.32	97.66	98.58
F6	82.21	83.49	90.52	91.24	95.38	98.32
F7	78.67	81.63	83.90	85.93	88.08	93.66
F8	80.66	82.57	86.59	89.08	91.82	93.79
F9	75.90	78.90	83.94	86.89	92.29	96.53

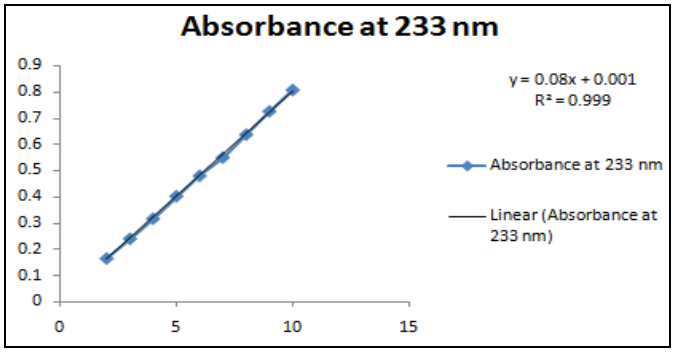

FIG. 9: CALIBRATION CURVE

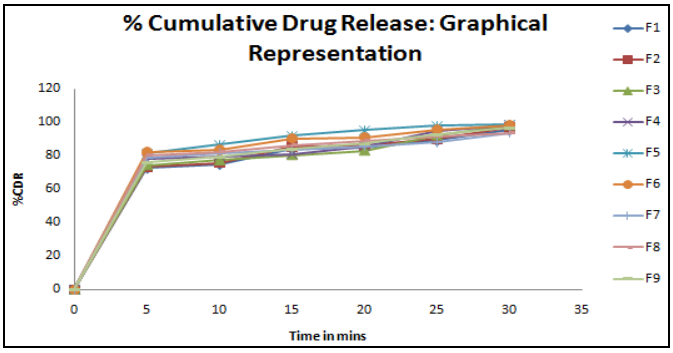

FIG. 10: DRUG RELEASE

Evaluation Parameters of Blend:

TABLE 15: EVALUATION PARAMETERS OF BLEND

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density (g/cm^3)	0.54	0.54	0.55	0.55	0.55	0.55	0.54	0.54	0.54
Tapped density(g/cm^3)	0.64	0.64	0.63	0.63	0.63	0.63	0.64	0.64	0.64
Angle of repose (degrees)	33.0	30.0	30.1	31.7	32.6	32.2	33.0	30.1	30.1
Compressibility index (%)	15.62	15.62	12.69	12.69	12.69	12.69	15.62	15.62	15.62
Hausner's ratio	1.185	1.185	1.145	1.145	1.145	1.145	1.185	1.185	1.185

Evaluation Parameters of Formed Tablets:

TABLE 16: EVALUATION PARAMETERS OF FORMED TABLETS

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness	4±0.33	4±0.32	3±0.24	4±0.25	4±0.23	3±0.34	2±0.29	2±0.12	2±0.15
Friability (%)	0.2	0.6	0.2	0.4	0.4	2	1.6	1	0.8
Wetting time (sec)	51.67	48.32	36.77	29.93	26.66	26.60	23.11	20.70	12.43
In-vitro dispersion time (sec)	49.86	46.33	45.90	43.29	15.60	14.54	11.22	9.08	6.20
Disintegration time (sec)	15.71	15.02	13.90	12.58	11.03	11.13	10.01	9.02	7.25
Drug content (%)	95.76	96.35	95.98	96.34	97.82	96.24	96.1	95.82	95.63

DISCUSSION: Diabetes has slowly emerged as a global epidemic affecting millions of people worldwide. The disease or to be more precise, the metabolic disorder, affects people of all ages. The main aim of management of diabetes is restoring of normal glucose levels within the body. Various chemical entities have been developed so as to achieve the desire goal of achieving normal glycemic conditions in the blood some of the prominent classes of drugs include biguanides, glitazones, sulfonylureas and α- glucosidase inhibitors however almost all of them are associated with certain side effects, however Metformin HCl a prominent member of the biguanide class has been thought to be drug of first choice in diabetes management as major side effects associated with Metformin include gastro-intestinal disturbances which fade off upon prolong use of the medication. Serious events as keto-acids has been reported to be caused due to Metformin therapy, however the occurrence of such an event is rare.

The present work is a study on orodispersible tablets. The powder required for manufacturing of the tablet has been shifted so as to ensure uniformity of the blend also, finely shifted powder grand for excellent tablet raw material. The role of binder and super disintegrants are very important in the formed tablets as both have opposite effects on the formed dosage forms; while binders hold the tablet particles, super disintegrants facilitate breaking of the tablet. In the study performed, batches F1, F2, F3 and F4 shows good results. Batches F1-F4 shows prolonged period of wetting time when compared to batches F6-F9. Batches F6-F9 shows rapid *in-vitro* dispersion time when compared to batches F1- F4. The batch F5 shows the optimum level of binder and super disintegrant. The batch F5 shows rapid disintegration and *in-vitro* dispersion as the super disintegrant added (TAG) is in quantity enough to facilitate the breaking of the tablet upon coming in contact with the disintegrating medium while the physical strength of the tablet is kept intact. It is also observed that super disintegrants work well only within a range beyond which tend to depreciate their activity. The prepared formulation has to be kept in mouth so as to disintegrate so addition of sweetener (mannitol) is necessary so as to impart the tablet pleasant mouth feel and taste.

Orodispersible tablets have proven advantageous in comparison to that of the conventional tablets as rapid disintegration of the dosage forms ensures rapid release of the drug also, the drug is absorbed quickly as the drug upon coming in contact with the buccal fluids mainly saliva, disintegrates and as the saliva passes down the gut a greater fragment of the drug in the saliva ids absorbed too. Super disintegrants form the main excipient behind the orodispersible tablets out of various synthetic and natural super disintegrants available, treated agar (TAG) was chosen due to easy availability and bio-compatibility.

Orodispersible tablets offer a promising future as rapid onset of action of the drug is obtained. The tablet proves a boon for those patients who have very limited access to water or those who are travelling. Certain parts of the population who may be unwilling to take the conventional tablet due to any of the reasons can also be the beneficiary to these unit dose systems. These systems also prove beneficial for people suffering from dysphagia or nausea. While ODT offer great possibilities the need for further improvements is still required.

CONCLUSION: Out of the 9 formulations developed the tablets made from the batch F5 with 6% super disintegrants was the most successful one. The obtained tablet from the F5 batch passed

in friability tests with a negligible loss (about 0.4%) of the weight of the tablet while tablets prepared from batches F7, F8 and F9 breaks. The obtained tablets F5was further evaluated for several other constraints and the obtained results further strengthen the candidature of F5 to be the best one. The disintegration time in water, was found to be 11.03 sec while the *in-vitro* dispersion time in simulated saliva fluid was found to be near about 15 sec. The percentage drug release of the tablets from F5 was further found to be astonishing as within a span of 30 min about 98.5% of the drug was released.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

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How to cite this article:
Bhardwaj P and Chauhan SB: formulation and evaluation of orodispersible tablets of Metformin hydrochloride using agar as natural super disintegrant. Int J Pharm Sci & Res 2018; 9(10): 4220-28. doi: 10.13040/IJPSR.0975-8232.9(10).4220-28.