Formulation Development of Fast Disintegrating Tablet of Metformin Hcl and Optimization of Disintegration Time and Friability by QbD Method

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Abstract:

Objective: to formulate and characterized fast disintegrating tablet of Metformin Hcl to produce intended benefits.

Methods: Tablets were prepared using a direct compression method employing superdisintegrants such as Sodium starch glycolate, Crosscarmellose Na, Microcrystalline cellulose. Tablets of Metformin Hcl prepared using sodium starch glycolate least disintegration time compare to Crosscarmellose Na, Microcrystalline cellulose

Results: An optimized formulation was found to have good hardness, wetting time, disintegrating time.F6 formulation is showing less friability and less disintegration time and drug release at constant rate as well as fast rate. Stability studies indicated that there are no significant changes in hardness, Percentage friability, drug content and in-vitro disintegration time and cumulative percentage drug release.

Conclusions: Thus it was concluded that by adopting a systematic formulation approach, Metformin Hcl fast disintegrating tablet could be formulated using superdisintegrants shows improved therapeutic efficacy. By direct compression method were found to be good and werefree from capping and chipping. Based on the in – vitro disintegration time, Formulation F6 were found to be promising and showed a dispersion time of 22 sec., wetting time of 48 and 64 sec respectively, which facilitate the faster dispersion in the mouth.

Keywords: Fast disintegrating tablet, Metformin Hcl, Sodium starch glycolate, Crosscarmellose Na, Microcrystalline cellulose.

Introduction: The oral route of drug administration is the most important route foradministering drugs for systemic effects. Except in certain cases the parenteral route is not routinely used for self administration, e.g. insulin. The topical route of administration has onlyrecently been employed to deliver drugs to the body for systemic effects. The parenteral routeof administration is important in treating medical emergencies in which the subject is comatoseor cannot swallow. Nevertheless, it is probable that at least 90% of all drugs used to provide systemic effects are administered by the oral route. When a new drug is discovered one of thefirst questions, a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by the oral route. Most of drugs that are administered orally,solid oral dosage forms represent the preferred class of products. Tablets and capsules representunit dosage forms in which usual dose of a drug has been accurately placed. [1, 2]

IDEAL PROPERTIES OF FAST DISINTEGRATING TABLETS (FDT):

- It should be quickly disintegrated within seconds when placed in the mouth.
- It should not require water to dissolve.

- Being a unit dosage form it should provide accurate dosing.
- Quick dissolution and absorption in the oral cavity.
- Easy to transport.
- Tablets are manufactured with conventional equipment within low cost.
- Less sensitive to environmental condition like humidity and temperature.It should less fragile and should maintain its hardness.[3,4]

ADVANTAGES OF FAST DISINTEGRATINGTABLETS:

- Fast Disintegrating Tablets (FDT) are a solid unit dosage form, so it provides accurate dosing, high drug loading is allowed in it, and it is an ideal dosage in case of geriatric and pediatric patients and also it is an ideal alternative of conventional tablet.
- It has fast action, as it is taken by the patient, it gets starts melting when it comes in contactwith saliva it rapidly absorbed in the oral cavity, it rapidly melts and produces quick action.
- Due to pregastric absorption the bioavailability of the drugs is improved, and less dose is required, which improves the patient compliance, clinical reports is also improved.
- FDTs does not require water to swallow and also it can be taken anywhere at any time, it isa convenient option for travelling patients and busy peoples who do not have immediate access of water hence patient compliance is improved.
- It is very easy and convenient to administer as it is a solid unit dosage form, it is mainly convenient for geriatric, pediatric uncooperative patients and dysphagic patients.
- FDTs are very safe and easy to swallow because there is no risk of suffocation in the airwaysdue to physical obstruction during swallowing.
- FDTs content stays minimal and it completely dissolves in the mouth, no residue is left so provide a good mouth feel hence improved palatability of the tablet.
- FDTs are less sensitive to environmental condition, hence they are very stable.
- FDTs are packed in simple blister packaging and there is no need of special and costly packaging, so that they are economical.
- FDTs provide new business avenues as product differentiation, product promotion, line extension, uniqueness, and life cycle management.
- FDTs are cost effective, it does not require costly ingredients, natural polymers when usedas exponent are available easily and at low cost and also it does not require special packaging material it can be packed in simple blister packs.
- It is a versatile technology as it is used in the development of OTC medicines, Rx medicines and veterinary medicines. [5,6,7]

SUPERDISINTEGRANTS:

Disintegrating agents are substances routinely included in the tablet formulations to aid in thebreak-up of the compacted mass into the primary particles to facilitate the dissolution or the release of the active ingredients when it is put into a fluid environment. They endorse moisturepenetration and dispersion of the tablet matrix. The major function of disintegrants is to opposethe efficiency of the tablet binder and physical forces that act under compression to structure the tablet.[8]

Recently new materials termed as “Superdisintegrants” have been developed to improve the disintegration processes. Superdisintegrants are another version of super-absorbing materials with tailor-made swelling properties. These materials are not planned to absorb significant amounts of water or aqueous fluids, but planned to swell very fast. Superdisintegrants are usedas a structural weakener for the disintegrable solid dosage forms. They are physically dispersedwithin the matrix of the dosage form and will expand when the dosage form is exposed to the wet environment.

These newer substances are more effective at lower concentrations with greater disintegratingefficiency and mechanical strength. Superdisintegrants are generally used at a low level in thesolid dosage form, typically 1 - 10 % by weight relative to the total weight of the dosage unit.

Their particles are generally small and porous, which allow for rapid tablet disintegration in the mouth without an objectionable mouth-feel from either large particles or gelling.
The particles are also compressible, which improves tablet hardness and its friability. Effective Superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. Generally, onegram of superdisintegrant absorbs 10-40 g of water or aqueous medium. After absorption, swelling pressure and isotropic swelling of the superdisintegrant particles create stress concentrated areas where a gradient of mechanical properties will exist due to which whole structure will break apart as shown in fig. 1 [9]

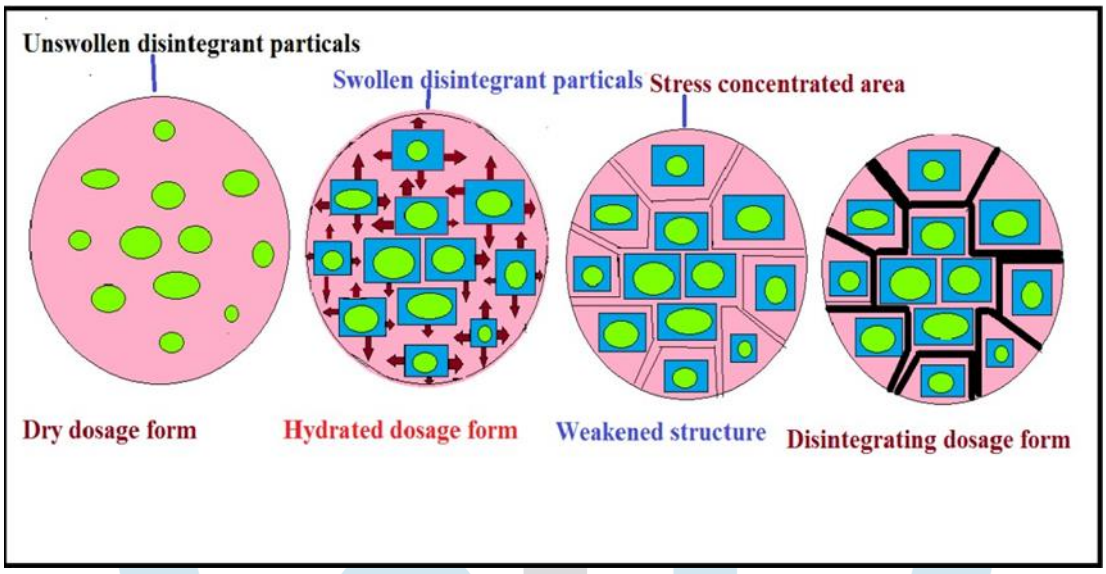


Figure no.1: Superdisintegrants MECHANISM OF SUPERDISINTEGRANTS:

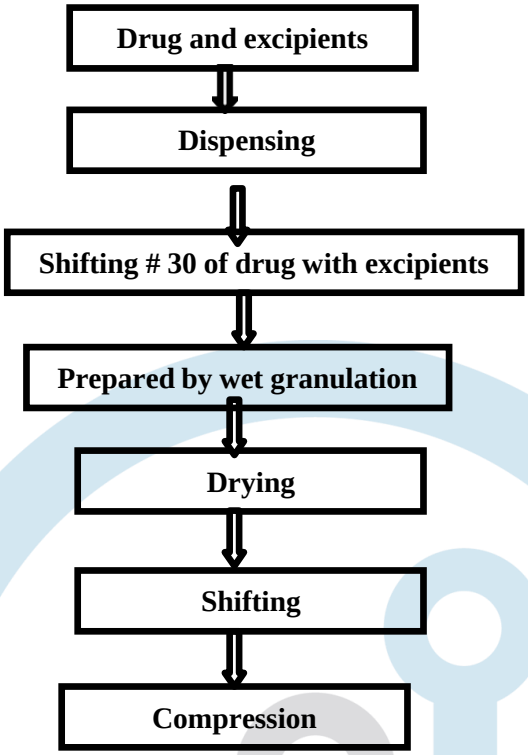
Superdisintegrants are used to improve the efficacy of solid dosage forms. This is achieved by various mechanisms. The mechanism by which the tablets break into small pieces and then produces a homogeneous suspension is based on: [12]

- Swelling
- Porosity and capillary action (Wicking)
- Particle repulsive forces
- Deformation recovery
- Chemical reaction (Acid-Base reaction)
- Heat of wetting
- Enzymatic reaction

MATERIALS AND METHODS:

Metformin Microcrystalline cellulose in Hcl was a present sample from Aquatic Formulation, Mumbai, Crosscarmellose Sodium, Mannitol, Aerosil , Magnesium Stearate was produced by Aquatic Formulation, Mumbai ,Sodium Starch Glycolate, Aspartame, Potassium dihydrogen phosphate was produced by Research-lab Fine Chem. Industries, Mumbai, Dried Starch Modern Science App. PVT. Ltd. Nashik.

General Method of preparation (Batch F1-F6)



All the ingredients were passed through 60 mesh sieve separately. The drug and microcrystalline cellulose was mixed by a small portion of both each time and blending it to get a uniform mixture kept aside. Then the ingredients were weighed and mixed in geometricalorder and the tablets were compressed of 10mm size flat round punch to get tablet using MultiStation rotary punch tablet compression machine.

Table 1. Composition of Fast disintegrating tablet

Formulation table								
Formula (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Metformin HCl	100	100	100	100	100	100	100	100
SSG	50	70	50	70	70	70	50	50
CCNa	40	40	60	60	40	60	40	60
MCC	65	65	45	45	45	65	45	65
Dried starch	20	20	20	20	20	20	20	20
Aerosil	05	05	05	05	05	05	05	05
Aspartame	05	05	05	05	05	05	05	05
Magnesium stearate	05	05	05	05	05	05	05	05
Mannitol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight (mg)	400	400	400	400	400	400	400	400

Evaluation parameters:

Pre-compression Parameters The essential prerequisites for determining if certain material wasacceptable for the desired formulation were the pre-compression characteristics. The different officially needed pre-compression characteristics that had to be identified were bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose for dosage form formulation.

Post-compression Parameter:

1) Thickness

2) Hardness

3) Friability

4) Disintegration time

5) Weight variation test

6) In vitro dissolution test

RESULT AND DISCUSSIONS

UV Spectroscopy:

The spectrum is shown in figure 2

Table No. 2 Wavelength of maximum absorbance (λ_{max}) in water as a solvent.

Solvent	λ_{max} (nm)
Phosphate buffer6. 8	234

In UV spectroscopy study, the maximum wavelength (λ_{max}) of Metformin HCl in phosphate buffer was found to be 234 nm. The reported λ_{max} of Metformin HCl water solvent is 234 nm

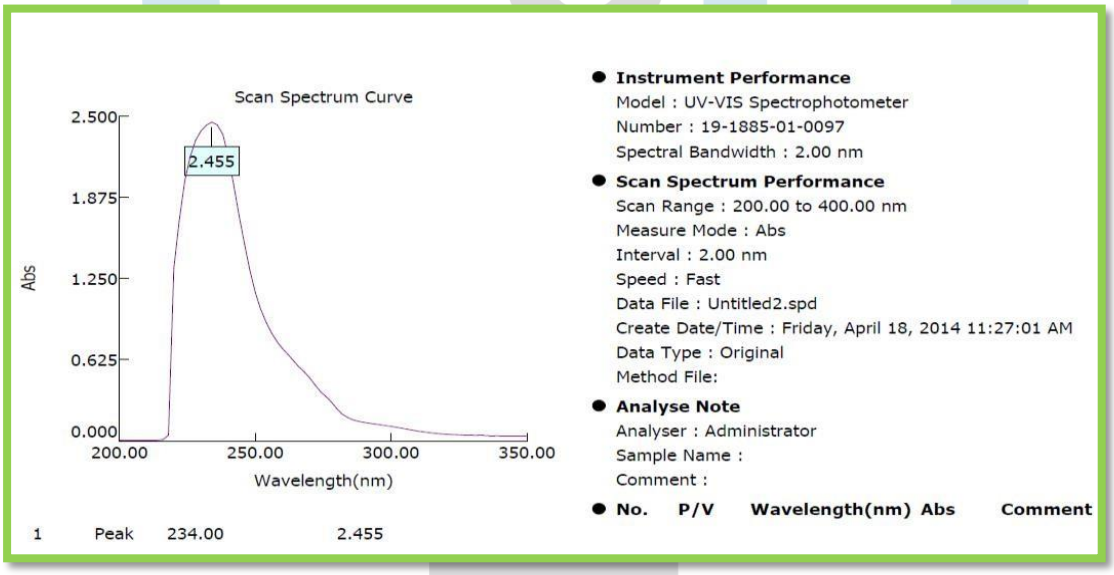


Figure 2: **UV Spectrum of Metformin HCl in phosphate bufferStudy of Beers-Lambert's Law:**

Calibration Curve of Metformin HCl in Phosphate Buffer:

The calibration curve of Metformin HCl was performed on Phosphate buffer. The calibration curve was found to be linear in the concentration range of 5-25 µg/ml having a coefficient of regression value $R^2 = 0.989$ and line equation, y = 0.036x – 1.853.

Table No.3: Concentration and Absorbance values for Metformin HCl in Phosphatebuffer (λ_{max} 234 NM)

Sr.No.	Concentration	Absorbance
1	5	2.036
2	10	2.191
3	15	2.455
4	20	2.576
5	25	2.763

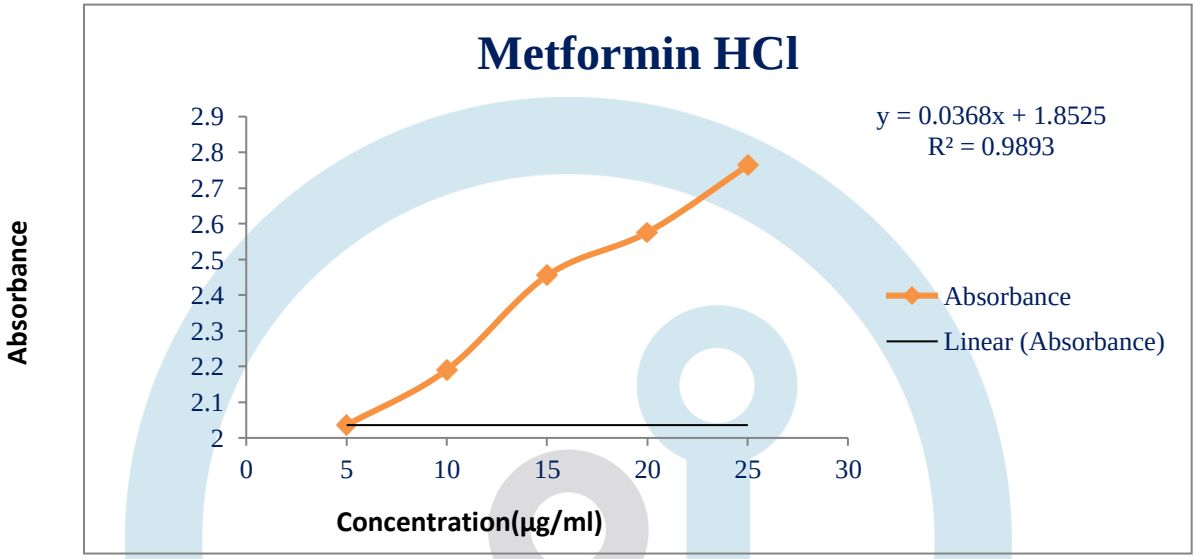


Figure 3: Beers-Lambert's plot for Metformin HCl in Phosphate buffer

FT-IR spectrum of Metformin HCl:

The FTIR spectrum of pure Metformin HCl showed peaks in wave numbers (cm-1) which corresponds to the functional group present in the structure of the drug. FT-IR spectrum of Metformin HCl is shown in fig. 4

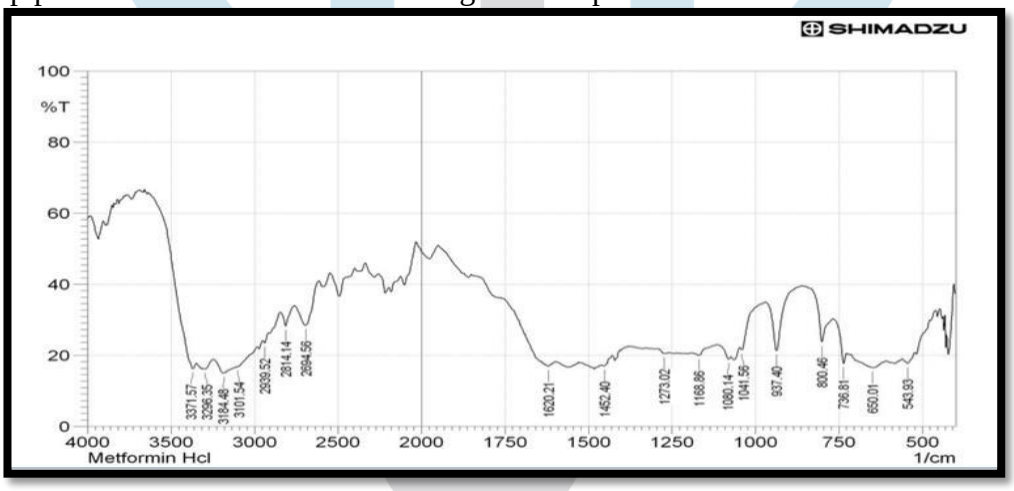


Figure No.4: FT-IR spectrum of Metformin HCl

Table 4: Identification of functional groups in FT-IR spectrum of Metformin HCl

Type of vibration	Class of compound	Frequency (1/cm)
C-H (Stretching)	Alkanes	2939.52
C-N (Stretching)	Primary Amine	1452.40
C=N (stretching)	Imines	1620.21
N-H (stretching)	Primary amine	3371.57
C-Cl (stretching)	Halogens	736

Differential Scanning Calorimetry (DSC):

Thermal analysis of drugs was carried out using DSC. The DSC curve of Metformin HCl profiles a sharp exothermic peak at 230.91^{0}C corresponding to its melting, and indicating its crystalline nature and purity of the sample. The heat required for melting was -808.07 mJ. TheDSC thermo gram is shown in fig. 5

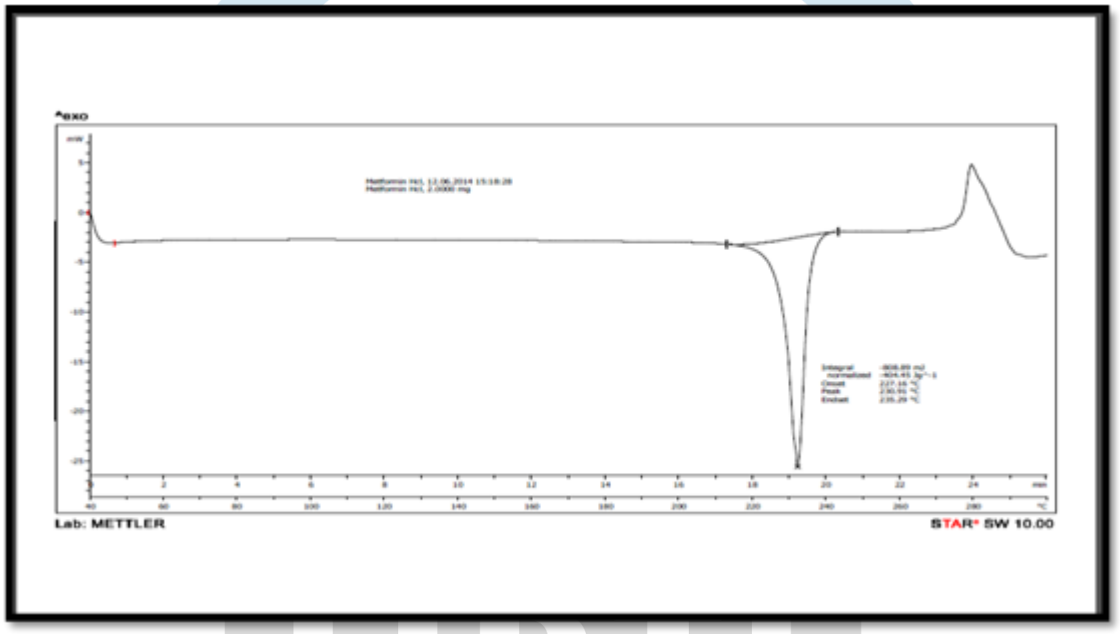


Figure 5: DSC of Metformin HCl

FT-IR spectrum:

The drug and polymer mixtures were taken in a sampler and the spectrum was recorded byscanning in the wavelength region of 4000-400 cm-1 using FTIR spectrophotometer.

FT-IR spectrum of Metformin HCl and cross carmellose sodium

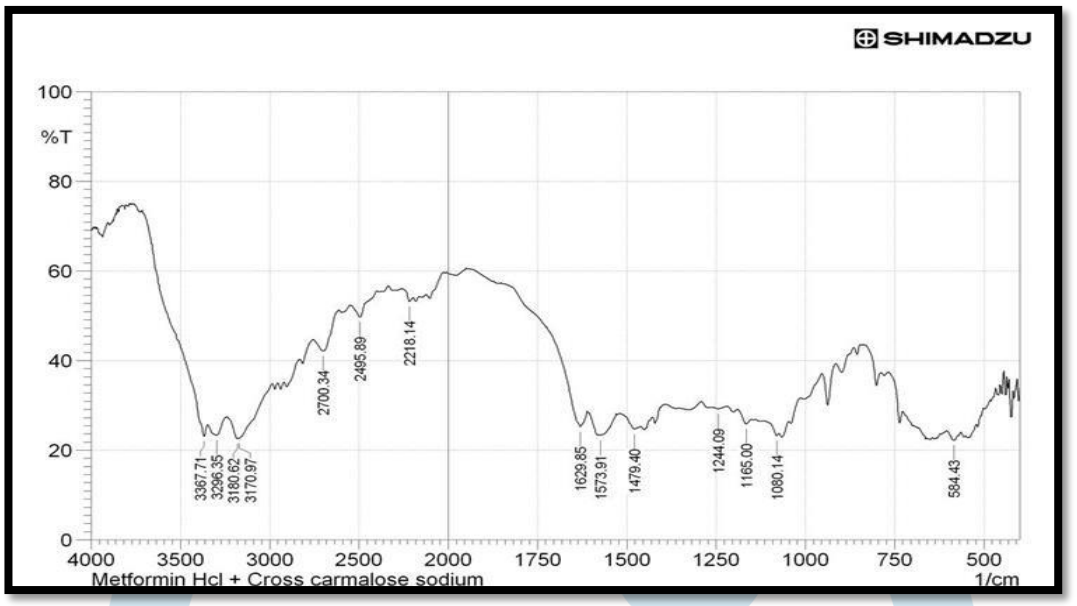


Figure 6: FT-IR of spectrum of Metformin HCl+ Crosscarmellose sodium

Table No. 5: Identification of functional groups in FT-IR spectrum of Metformin HCland crosscarmellose sodium

Type of vibration	Class of compound	Frequency (1/cm)
C-H (Stretching)	Alkanes	2939.52
C-N (Stretching)	Primary Amine	1452.40
C=N (stretching)	Imines	1620.21
N-H (stretching)	Primary amine	3371.57
C-Cl	Halogens	736
O-H broad(stretching)	Hydroxyl	3367
C=O	Carbonyl	1629
C-O-C	Ether	1165

FT-IR spectrum of Metformin HCl and microcrystalline cellulose

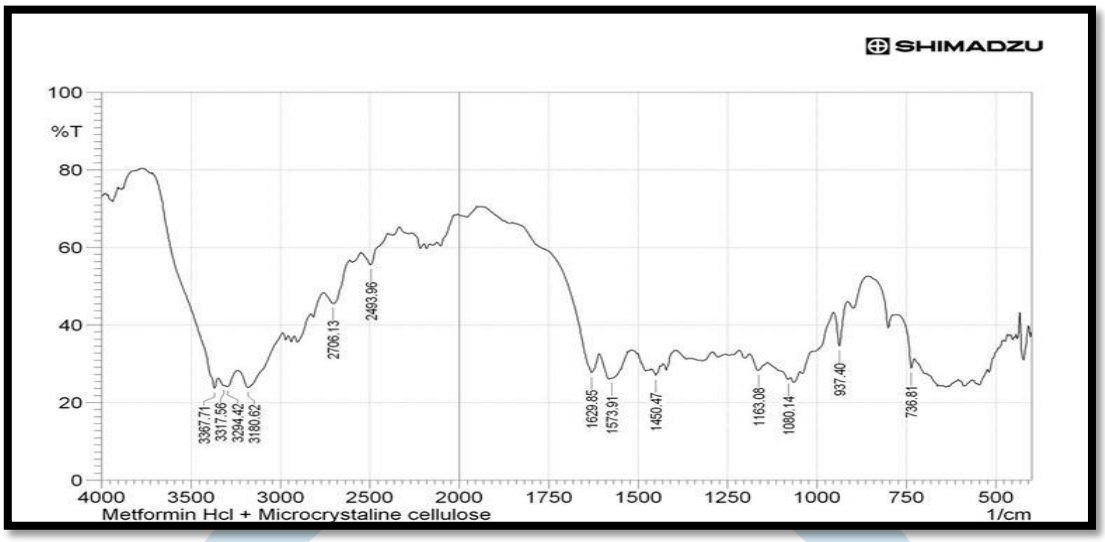


Figure 7: FT-IR of the spectrum of Metformin HCl +Microcrystalline cellulose

Table 6: Identification of functional groups in FT-IR spectrum of Metformin HCl andmicrocrystalline cellulose

Type of vibration	**Class of compound**	**Frequency (1/cm)**
C-H (Stretching)	Alkanes	2939.52
C-N (Stretching)	Primary Amine	1452.40
C=N (stretching)	Imines	1620.21
N-H (stretching)	Primary amine	3371.57
C-Cl	Halogens	736
O-H free (stretching)	Hydroxyl	3367
C-H stretching	Methylene	2706
C-O-C	Ether	1165

FT-IR spectrum of Mixture 01 containing microcrystalline cellulose

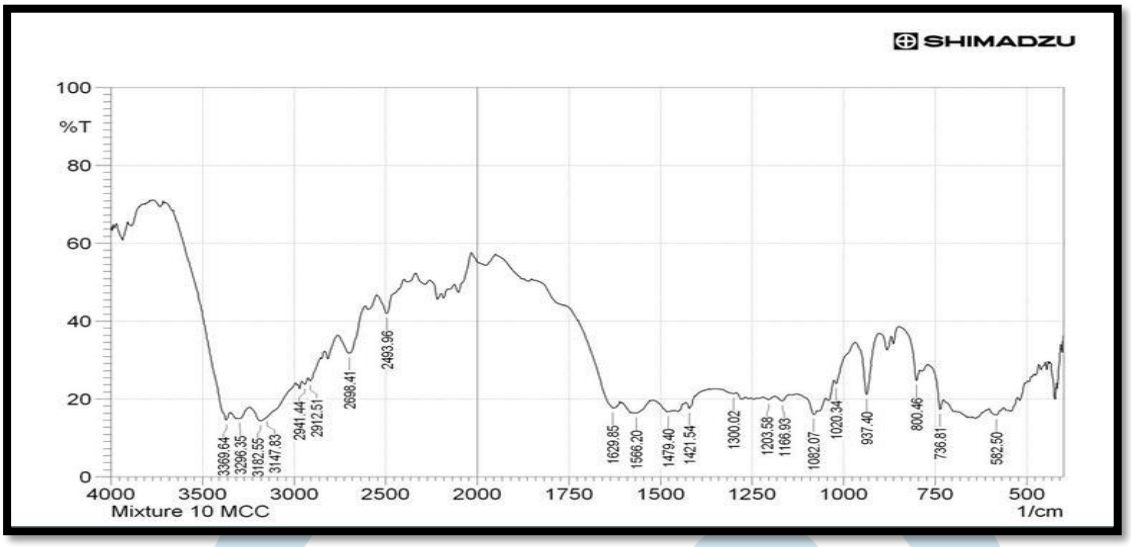


Figure 8: FT-IR of the spectrum of Mixture containing microcrystalline cellulose

Table No. 7: Identification of functional groups in FT-IR spectrum of Mixture 01containing microcrystalline cellulose

Type of vibration	Class of compound	Frequency (1/cm)
O-H broad(stretching)	Hydroxyl	3373
C-O-C	Ether	1165

FT-IR spectrum of Mixture 01 containing microcrystalline cellulose

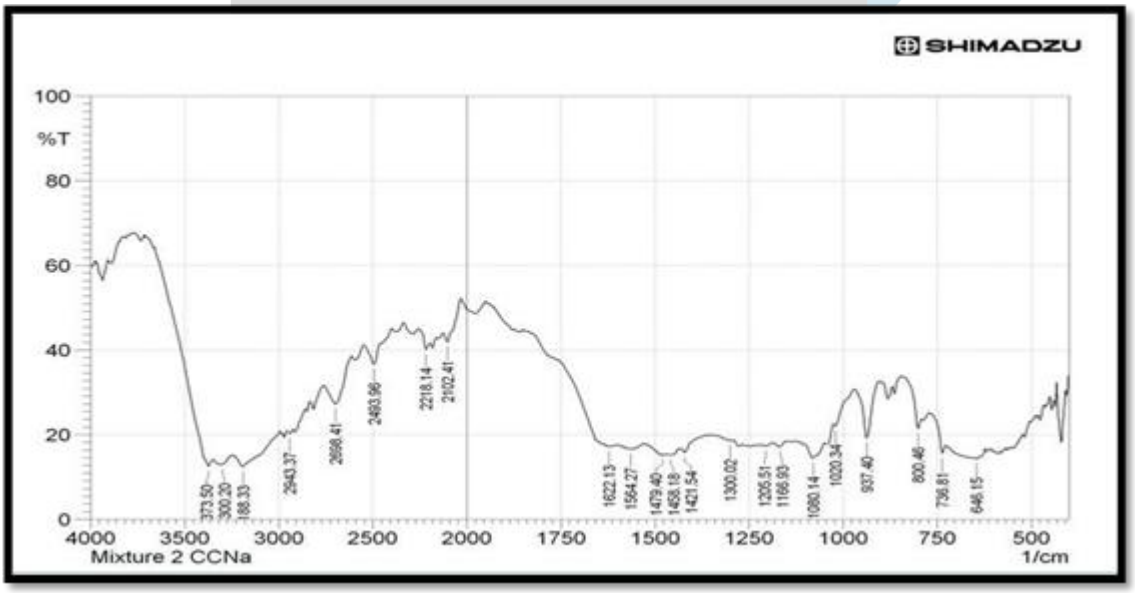


Figure 9: FT-IR of the spectrum of Mixture containing crosscarmellulose sodium

Table No.8: Identification of functional groups in FT-IR spectrum of Mixture 02containing Crosscarmellulose sodium

Type of vibration	Class of compound	Frequency (1/cm)
O-H broad(stretching)	Hydroxyl	3373
C=O	Carbonyl	1629
C-O-C	Ether	1165

DIFFERENTIAL SCANNING CALORIMETRY (DSC):

Thermal analysis of drug and microcrystalline cellulose was carried out using DSC. The DSC curve of Metformin HCl and microcrystalline cellulose profiles a sharp exothermic peak at 233.60^{0}C corresponding to its melting, and indicating its crystalline nature and purity of the sample. The heat required for melting was -147.39 mJ. The DSC thermo gram is shown in fig.10

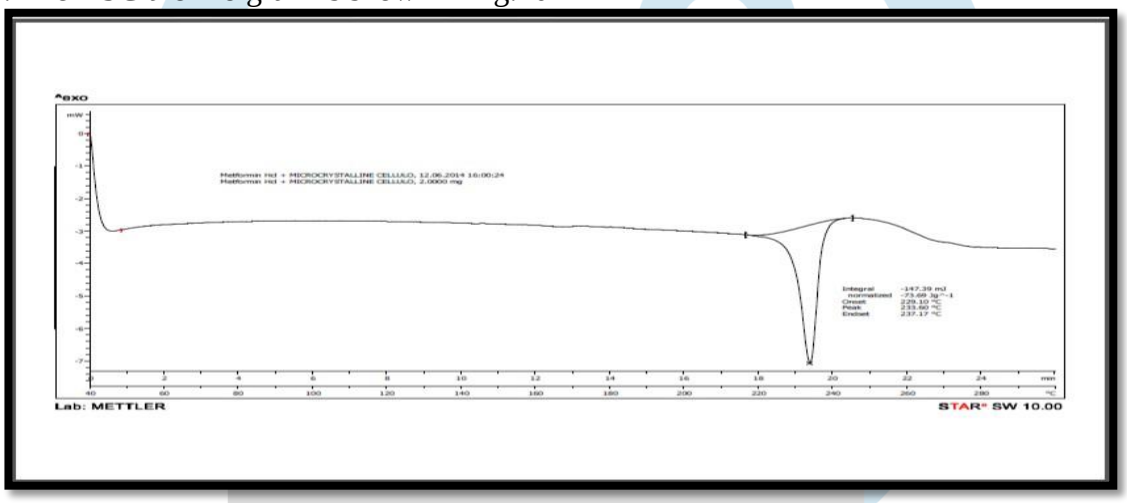


Figure 10: DSC of Metformin Hcl and microcrystalline celluloseDifferential Scanning Calorimetry (DSC):

Thermal analysis of drug and crosscarmellose sodium was carried out using DSC. The DSC curve of Metformin Hcl and crosscarmellose sodium profiles a sharp exothermic peak at 231.73^{0}C corresponding to its melting, and indicating its crystalline nature and purity of the sample. The heat required for melting was -512.44 mJ. The DSC thermo gram is shown in fig.11

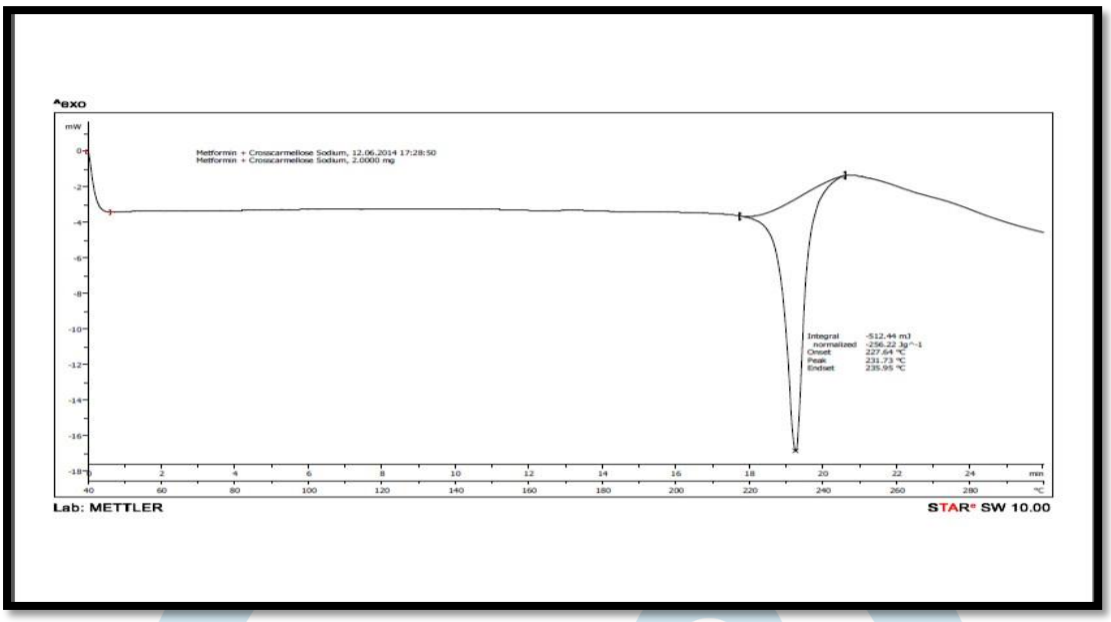


Figure 11: DSC of Metformin Hcl and crosscarmellose sodiumEVALUATION PARAMETERS:
Precompression Parameters:

Table 9 Precompression parameter (stage II):

Sr.No.	Angle of repose (degree)	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index (%)	Hausner's ratio	Bulkiness
F1	29.45	0.52	0.61	14.7	1.17	1.92
F2	27.32	0.59	0.65	13.0	1.15	1.69
F3	24.42	0.51	0.62	17.7	1.21	1.21
F4	27.20	0.53	0.60	11.6	1.13	1.80
F5	26.31	0.55	0.62	14.5	1.16	1.88
F6	25.19	0.59	0.67	11.9	1.13	1.96
F7	28.12	0.57	0.72	16.2	1.19	1.99
F8	26.89	0.59	0.79	15.7	1.24	1.72

PRE-FORMULATION STUDIES:

Angle of Repose (θ):
The data obtained from the angle of repose for all the formulations were found to be inthe range of $24^0.42`$ and $29^0.45`$. All the formulations prepared by both the methods showed the angle of repose less than 30^0, which reveals good flow property. As mentioned earlier in the literature. [1]
Bulk Density:

Loose bulk density (LBD) and tapped bulk density (TBD) for the blend was performed.The loose bulk density and tapped bulk density for the entire formulation blend varied from

0.51 mg/cm^3 to 0.59 mg/cm^3 (direct compression method)

Hausner Ratio:

Hausner ratio of the entire formulation showed Between 1.13 to 1.24 indicates better flow properties [1]

Carr's Consolidation Index:

The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 11.06% to 17.09%. The directly compressible granulations hadshown excellent compressibility index values up to 15% result in good to excellent flow properties. As shown in previous research work. [1]

POST COMPRESSION PARAMETER:

Table 10: Post compression parameter:

Sr.No.	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Drug content (%)	Wetting time (s)	Water absorption ratio (%)	Disintegration time (s)
F1	390	2.90	0.45	97.9	59±0.15	1.3	37
F2	380	3.07	0.34	98.9	53±0.25	1.5	23
F3	410	2.94	0.37	99.5	61±0.17	0.53	31
F4	390	3.01	0.32	100.1	51±0.21	0.66	28
F5	390	2.8	0.29	98.7	48±0.17	1.0	32
F6	400	3.01	0.25	99.6	50±0.14	1.2	22
F7	390	3.08	0.36	98.3	49±0.16	1.4	33
F8	390	3.02	0.41	97.4	64±0.19	1.2	26

Hardness:

Tablet crushing strength, the critical parameter was controlled as the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling beforeusage, depends on its hardness. Hence, hardness for all formulation batches prepared by direct compression method was found to be between 2.08 and 3.07 Kg/cm^2. This finding wasobserved due to constant tablet press setting across all batches, irrespective of weight variation.

Friability:

To achieve % friability within limits for a fast disintegrating tablet is a challenge to theformulator since all methods of manufacturing of fast disintegrating tablet are responsible for increasing the % friability values. The % friability values for all formulation batches preparedby direct compression method was found to be between 0.29 and 0.45 % This was also observed due to constant tablet press setting across all batches.

Average Weight:

As material was free-flowing, tablets were obtained of uniform weight due to uniformdie fill with an acceptable variation as per I.P. Standards. The weight variation was found in all designed formulations in the range 380 to 410 mg. All the tablets passed the weight variation

test as the average percentage weight variation was within 7.5% i.e. in the pharmacopoeialimits.

In vitro Disintegration Time:

Disintegration, the first important step for a drug absorption from a solid dosage form after oral administration was preliminarily focused. It was reported that tablet disintegration was affected by the particle size, the degree of substitution, and extent of cross-linkage. An important factor affecting the disintegration is the tablet hardness and/or the compaction forceused in making the tablet hardness. The hardness of the tablet has an influence on the disintegration time as it affects the porosity of the matrix and, accordingly, the ability of water to penetrate through the matrix. All tablets disintegrated rapidly without a disc in the IP test, especially when used at optimum concentrations of selected superdisintegrants.
The *in vitro* disintegration time of Metformin HCl prepared by direct compression method were found to be in the range of 22 to 37 Sec fulfilling the official requirements.

Wetting Time

Wetting time is another important related inner structure of tablet & parameter to waterabsorption ratio, which needs to be assessed to give an insight into the disintegration propertiesof the tablets. Wetting time for all formulation batches prepared by direct compression methodshowed wide variation in the range of 5.1 and 6.4 seconds. This wide variation range was observed due to developmental changes in formulation.
Water Absorption Ratio:

The formulations prepared by direct compression method the technique shows the waterabsorption ratio in the range 0.66 to 1.4 %

Uniformity of Drug Content:
The percent drug content of all the tablets was found to be in the range of 97.04 to

100.01 percent.

%Drug Release:

Table 11: Release profile of formulations of Metformin HCl

Time in min	% Drug Release			
	F1	F2	F3	F4
5	30.14	32.63	35.11	35.06
10	39.02	43.25	43.34	44.11
15	51.13	53.42	68.44	50.00
20	69.15	74.03	76.82	67.91
25	82.07	84.33	87.12	85.45
30	90.10	91.94	94.11	92.73

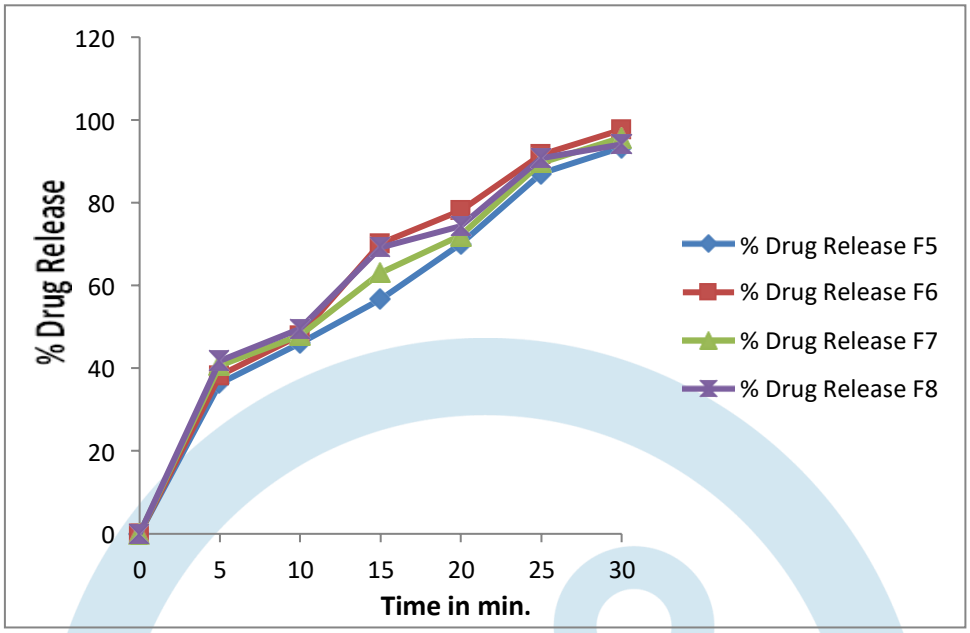


Figure 12: %drug release F1 toF5

Table 13: Release profile of formulations of Metformin Hcl

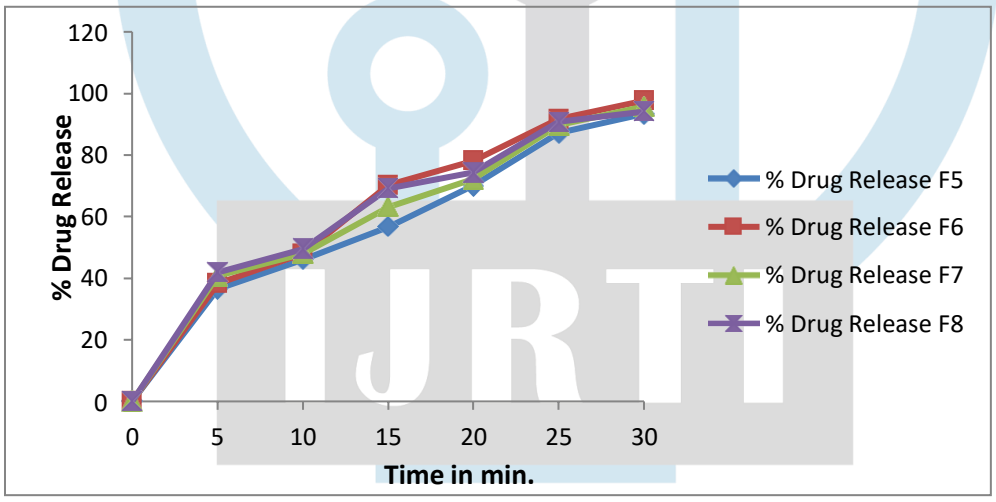


Figure 13: %drug release F5 to F8

In Vitro Dissolution Study:

The merely disintegration test is not judicious since all superdisintegrants appear highly efficient, with disintegration times as less than 25 seconds when used in different desired concentrations. However, as discussed above, differences in the particle size generated in the disintegrated tablets could affect drug dissolution since breaking the tablets into finer fragmentsmay promote drug dissolution by providing larger total surface areas for drug dissolution to take place.

In case of tablets prepared by direct compression technique the % drug release values increased with an increase in the concentration of crosscarmellose sodium, microcrystalline cellulose and sodium starch glycolate. The rapid increase in dissolution of Metformin HCl withthe increase in crosscarmellose sodium may be due to rapid swelling and disintegrating tabletsrapidly into apparently primary particles. With sodium starch glycolate, disintegrate by the rapid uptake of water, followed by rapid and enormous swelling into primary particle, but moreslowly due to the formation of a viscous gel layer by sodium starch glycolate. Thus the

difference in the size distribution generated with different superdisintegrants might have contributed to the difference in the % drug release values with the same amount of superdisintegrants in the tablets.

RESULT OF STABILITY STUDY:

The promising formulation were subjected to short term stability study by storing the Formulations at 40°C/75% RH up to three month. The formulations F6 were selected. After three month the tablets were again analyzed for the hardness, friability, drug content uniformity and dispersion time.

Table 12: Result for stability at 40°C/75% RH for 3 months

Sr. no.	Formulation	Hardness Kg/cm^2	Friability %	Disintegration time(Sec.)	% drug release
1	F6	3.4	0.28	20	98.31

: Stability Studies:

The promising formulations were subjected to short term stability study by storing the formulations at 25°C/65% and 40°C/75% RH up to three month. The formulation F6 was selected. After three month the tablets were again analyzed for the hardness, friability, drug content uniformity and dispersion time. The increase in the disintegration time was observed in case of tablets prepared with direct compression method. This may be due to increase in thehardness of the tablets during storage; whereas 90 days and 45^{o}C were used during stability studies. No change was observed in the disintegration time and hardness of tablets. No significant change was observed in the drug content of formulation.

CONCLUSION:

In the present work Fast Disintegrating tablets of Metformin HCl were prepared by direct compression method using superdisintegrants such as sodium starch glycolate, crosscarmellose sodium and microcrystalline cellulose.

All the tablets of Metformin HCl were subjected to weight variation, hardness,friability, *in vitro* dispersion, drug polymer interaction, drug content uniformity, water absorption ratio, wetting time, and *in vitro* drug release.

Based on the above studies following conclusions can be drawn:

- Tablet prepared by direct compression method were found to be good and were free from chipping and capping.
- Lower values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared.
- The hardness of the prepared tablets was found to be in the range of 2.90 to 3.08 Kg/cm^2.
- The friability values of the prepared tablet were found to be less than 1%.
- IR spectroscopic studies indicated that the drug is compatible with all the excipients.
- The *in vitro* dispersion time of Metformin HCl prepared by direct compression method were found to be in the range of 22 to 37 Sec fulfilling the official requirements.

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