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"FORMULATION, DEVELOPMENT AND ABSORPTION ENHANCEMENT OF METFORMIN HYDROCHLORIDE BY USING SPRAY DRYING TECHNIQUE"

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ABSTRACT

The present study is to formulate an anti-diabetic tablet containing permeation enhancer which enhances gastrointestinal absorption of poorly absorbable anti-diabetic drug. Metformin hydrochloride (HCl) is a BCS class III drug which has high solubility and poor intestinal absorption characteristic. The gastrointestinal absorption of metformin hydrochloride was enhanced using permeation enhancer like cyclodextrin. The permeation of drug was measured by everted sac technique using chicken intestine. The drug was absorbed through chicken intestine mainly by passive diffusion mechanism. The absorbed drug was determined by using U.V Visible Spectrophotometer at 234nm. After analyzing the results it was found that cyclodextrin enhance the absorption of metformin hydrochloride from chicken intestine. This cyclodextrin was used to reduce dose of metformin hydrochloride in tablet dosage form. For optimizing the dose of metformin hydrochloride, different batches of different permeation enhancer were used and tablets were prepared by direct compression method with different concentration of permeation enhancer and metformin hydrochloride. Metformin hydrochloride exhibits poor compressibility during compaction, often resulting in weak and unacceptable tablets with a high tendency to cap. The purpose was to develop directly compressible metformin hydrochloride by the spray-drying technique in the presence of polymer. This help in increase in the flow property of metformin HCL. The permeability of this drug was increased by the addition of cyclodextrin which acts as a permeation enhancer. This in turn results in better absorption enhancement.

KEYWORDS: Metformin HCl, Spray drying, Permeation enhancer, Cyclodextrin, Everted sac method.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder, resulting from insulin deficiency, characterized by hyperglycemia, altered metabolism of carbohydrates, protein and lipids, and an increased risk of vascular complications. Predisposition to diabetes mellitus is inherited, although the genetic factors are complex. This is one of the most widely studied, researched and advance areas in the medical field. Millions of people have diabetes. Even children suffer from this disease. That is why I feel that we are fortunate that our disease has been diagnosed at right time. At present there is no cure in any of the apathies for this disease. But with modern medical advancement you can definitely live near normal healthy life. In normal patients Fasting plasma glucose is < 100 mg/dL and Random plasma glucose is < 130 mg/dL after diabetes it is ≥ 126 mg/dL and ≥ 200 mg/dL.[1,2,3,4]

Metformin HCL is an anti-hyperglycemic agent, which improves glucose tolerance in type II diabetes. It has been reported that the absolute bioavailability of Metformin HCL when given orally is 50–60%. Biological half-life of Metformin HCL is 1.5–1.6 h and the main site of its absorption is proximal small intestines. When a spray dried Metformin HCL is mixed with the permeation enhancer, then the drug would be available in the dissolved form at the main site of its absorption i.e., proximal small intestines. This would lead to improvement in the bioavailability of the drug. In this way it stands an advantage over sustained dosage form, which needs to be administered with a high dose twice a day.[6]

Spray drying is a unit operation in which a liquid stream (solution, suspension or emulsion) is continuously divided into very fine droplets (a process known as atomization) into a drying chamber. Once the droplets meet the warm air in the drying chamber they rapidly evaporate to form dry particles, which are separated from the drying gas using a cyclone or a bag-filter. Hence the spray drying process can be described as consisting of four events.[7,8]

i. Atomization of the liquid into droplets
ii. Contact of the droplets with the warm drying gas
iii. Rapid evaporation of the droplets to form dry particles
iv. Recovery of the dry particles from the drying gas, using a cyclone/filter

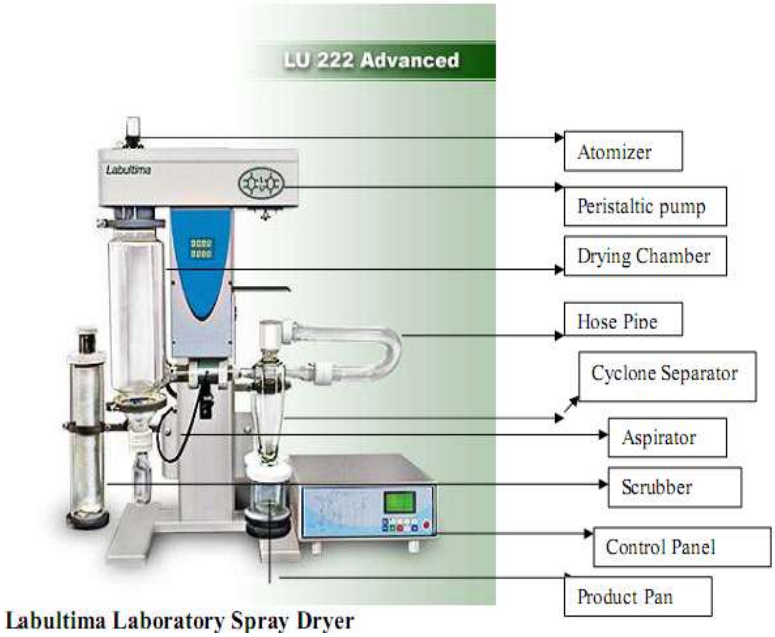

Fig.No.1: Schematic overview of a spray dryer.

Studied had been done to determine the barriers for the intestinal permeability of drugs. The location of these barriers may be in the unstirred water layer, the mucous layer, the apical and basal cell membrane and cell contents, the tight junctions and the wall of lymph and capillaries. Metabolic barriers of the mucosal peptidases are the other barriers which extensively condense the bioavailability of peptides and proteins.[9]

For this study intestinal absorption (permeability) studies are to be performed. These studies based on isolated intestinal sacs are routinely performed. To the best of our knowledge in vitro absorption studies using chicken intestine have less frequently used . So, in the present work chicken's small intestine was used for intestinal absorption studies of prepared tablets based on the assumption that membrane permeability of drugs is not species dependent since the composition of plasma membrane of intestinal epithelial cells is similar across the species.[9,10]

MATERIALS & METHODS

Metformin hydrochloride was provided as gift samples from Wockhardt pvt.ltd, Aurangabad. All other chemicals used were of analytical grade. The instruments used are eight station punching machine (chamunda), eight stage tablet dissolution apparatus (Electrolab, Mumbai), UV Spectrophotometer (Schimadzu, Japan), Fourier Transform Infrared spectrophotometer (FTIR) (Bruker).

METHODS

Preparation of absorption enhanced Metformin tablets

Table no. 10 enlists the composition of absorption enhanced Metformin oral tablets prepared using different absorption (permeation) enhancer. Lactose was added as filler, Crospovidone powder as disintegrant, talc as glidant and magnesium stearate as lubricant. Direct compression method is selected for tablet punching. The powder is compressed in to tablets (500mg) by using eight station punching machine.

Preparation of Spray dried Metformin HCL powder[30]

Spray-drying of Metformin HCL is done by mixing it with Sodium lauryl sulfate (SLS).Samples of Metformin HCL was dissolved in Methanol with SLS to increase the flow property of the drug. The ratio selected is 1:1 ratio of drug and SLS both dissolved in methanol and then run for spray drying of the solution. Spray-drying was carried out using Labultima – 222 spray dryer available in college. The product was collected form the collector bottle after the assembly was stopped. This powder was then used for the tablet formulation using permeation enhancer.

Spray-drying operating condition

- Inlet temperature - 180^{0}C
- Outlet temp. - 170 ^{0}C
- Cooling temp. - 110 ^{0}C
- Inlet High - 200 ^{0}C
- Outlet High - 190^{0}C
- Aspirator flow rate – 40 Nm3/ hrs.
- Feed flow rate – 1 ml/min.
- D Block ON -1 sec
- D Block ON -90 sec
- Cycle time – 400 min.

RESULT OF EXPERIMENTAL WORK

The immediate release tablets of Metformin HCL was prepared and evaluated for their use as Absorption enhancement of drug delivery systems to increase its bioavailability & permeation. In the present study, nine batches were optimized into three formulae and the composition of all the batches are shown in **Table No.10** respectively. The prepared tablet of Metformin HCL was evaluated for their pre-compression and post-compression parameters.

1.1. Preformulation study of Drug[18,19,20]

1.1 Colour

The sample of the drug Metformin HCL was found to be white crystalline powder. the color and odor complies with the description that is found in the literature.

1.2.Solubility

Table No. 1: Solubility Profile of Metformin HCL.

Sr. No.	Solvent	Solubility µg/ml
1.	Water	386.55
2.	6.8 pH phosphate buffer	515.64
3.	0.1 N HCL	493.00

1.3: Melting point

The melting point of the drug matched with the value found in literature.

Table No. 2: Melting Point of Metformin HCL

Drug	Melting Point range	
	Literature	Practical
Metformin HCL	223-226°C	224°C

1.4 : Assay

The percentage purity of given drug Metformin HCL was found to be 99.36% which complies the B.P standards.

1.5 : UV Spectroscopy[22,23,24]

1.5.1 Determination of λ_{max}

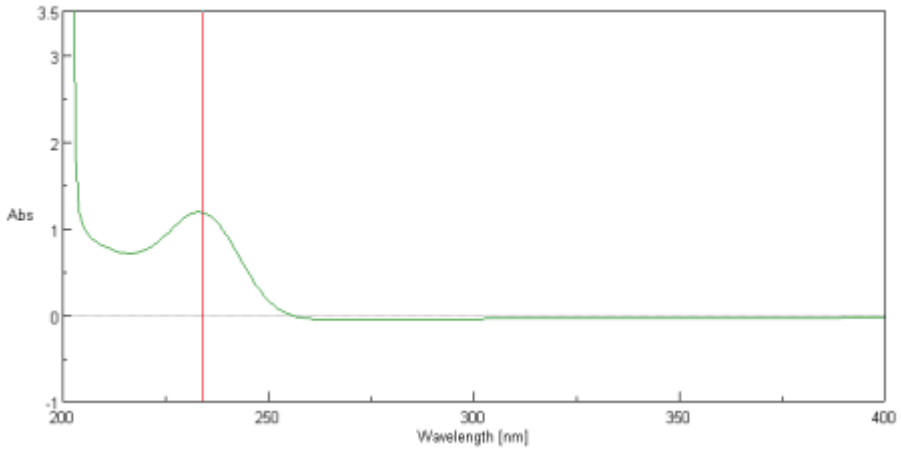

Fig. No. 1: UV Spectrum of Metformin HCL at 234 nm.

1.5.2. Calibration Curve of Metformin HCL in Distilled Water

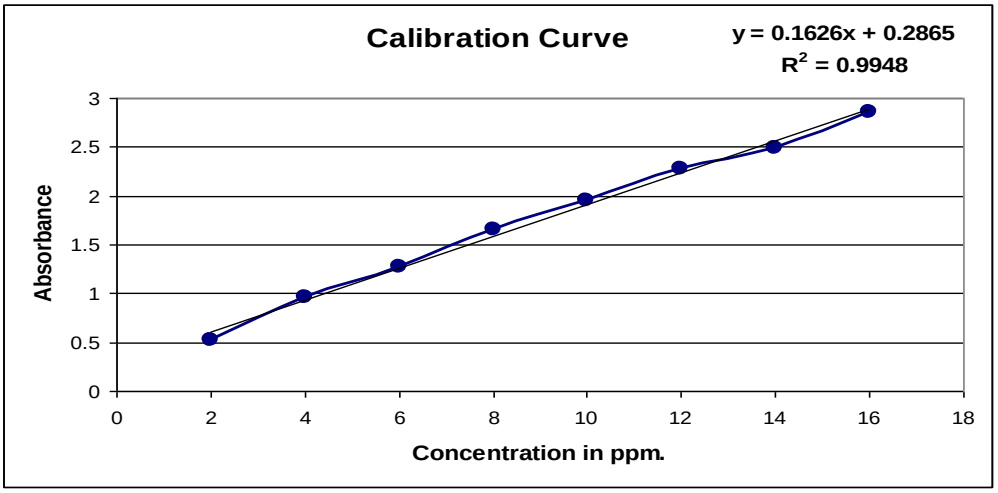

Fig. No. 2: Calibration curve of Metformin HCL in distilled water.

Calibration curve of Metformin HCL was performed in Distilled water. The calibration curves of Metformin HCL in this media was found to be linear in the concentration range of 2-16 µg/ml having coefficient of regression value R^2=0.9948 and slope is m= 0.1626.

1.5.3 Calibration Curve of Metformin HCL in Phosphate Buffer p^H-6.8

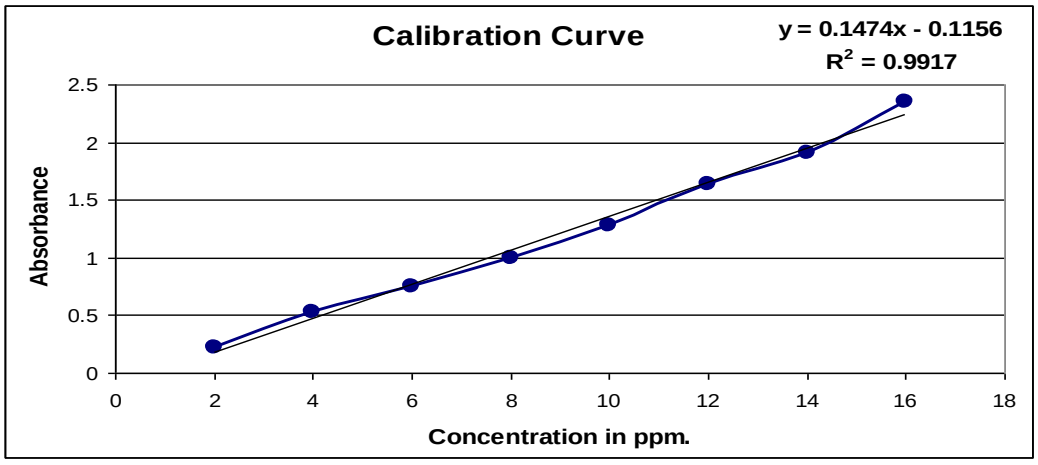

Fig. No. 3 : Calibration curve of Metformin HCL in phosphate buffer pH 6.8.

Calibration curve of Metformin HCL was performed in phosphate buffer pH 6.8. The calibration curves of Metformin HCL in this media was found to be linear in the concentration range of 2-16 µg/ml having coefficient of regression value R^2=0.9917 and slope is m= 0.1474.

1.5.3. Calibration Curve of Metformin HCL in 0.1 N HCL

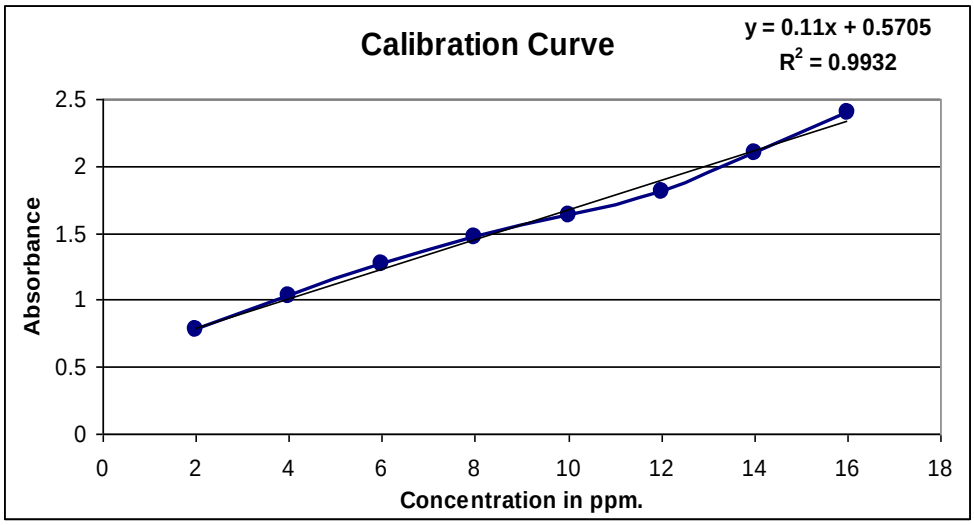

Fig. No. 4: Calibration Curve of Metformin HCL in 0.1 N HCL.

Calibration curve of Metformin HCL was performed in 0.1 N HCL. The calibration curves of Metformin HCL in this media was found to be linear in the concentration range of 2-16 µg/ml having coefficient of regression value R2=0.9932 and slope is m= 0.11.

6. Fourier Transform Infrared Spectroscopy (FT-IR)[23,24]

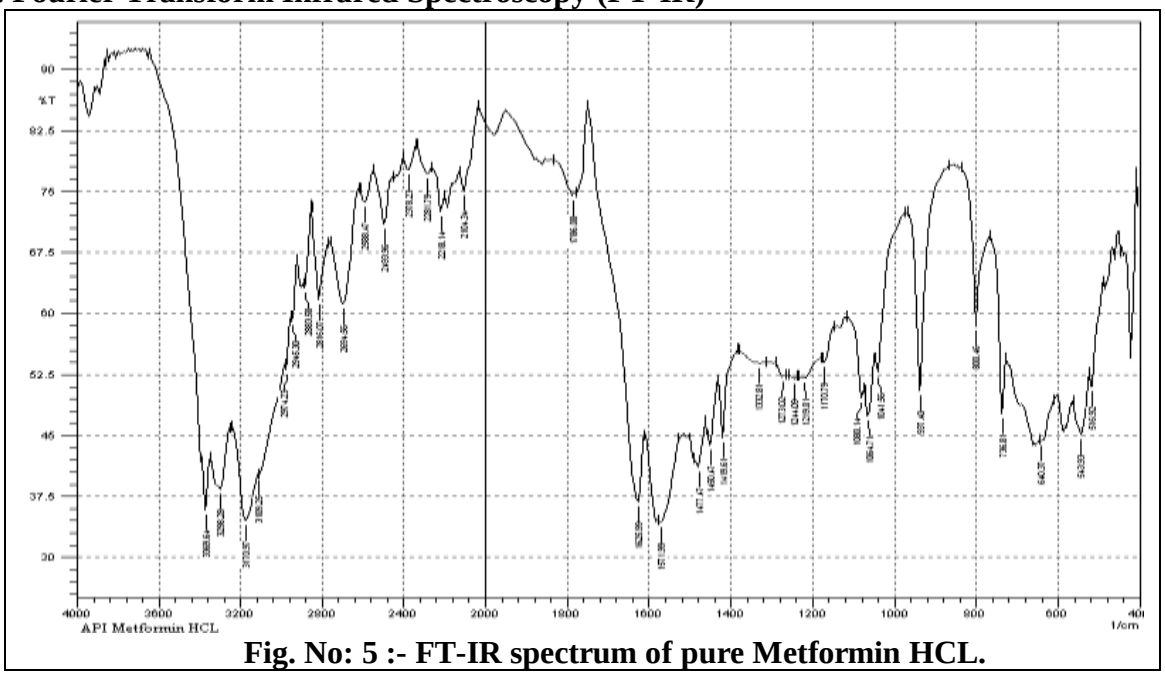

Fig. No: 5 :- FT-IR spectrum of pure Metformin HCL.

The FT-IR spectra of pure Metformin HCL shows peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug. The functional groups determined were similar to the values given in literature.

Table No. 3: FT-IR spectra of Metformin HCL

Sr. No.	Functional groups	Ranges cm $^{-1}$
1.	C-H Stretching	3170
2.	C-H bending	1450
3.	C-N stretching	1571
4.	C=N stretching	1625
5.	N-H stretching 1^0	3369
6.	N-H stretching 2^0	3298

The absorption bands shown by Metformin HCL are characteristic of the groups present in its molecular structure (**Fig. No. 5**). The presence of absorption bands corresponding to the functional groups present in the structure of Metformin HCL and the absence of any well-defined unaccountable peaks is a confirmation of the purity of the drug sample.

7. Differential Scanning Calorimetry (DSC)[25]

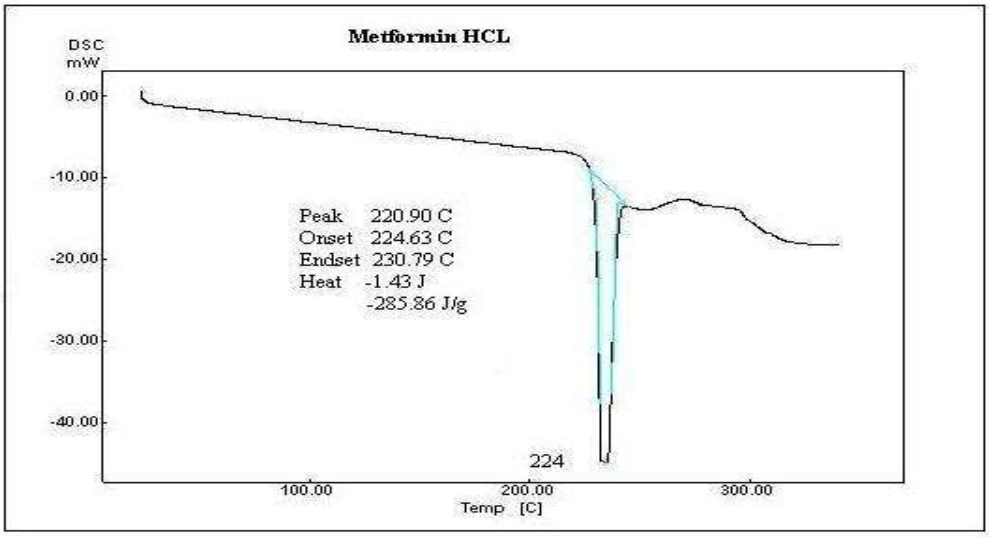

Fig. No. 6 : DSC thermogram of pure Metformin HCL.

The DSC thermogram of pure Metformin HCL shows a sharp endothermic peak at 224.63˚C which is characteristic of melting point of drug. The sharp endothermic peak also indicates crystalline nature of drug.The drug shows degradation peak above 300˚C. This data is useful for formulation of tablet. During formulation the degradation temperature of Metformin HCL was taken into consideration. This thermogram was also referred later to study interactions in formulation.

8. Scanning Electron Microscopy (SEM)[30]

SEM micrographs indicate needle-shaped and relatively large size crystals of metformin hydrochloride. The needle-shaped crystals of the untreated drug are responsible for its poor

compressibility, while the micrographs of the spray-dried drug show a reduction in size and change into an almost spherical shape. The spherical shape of the spray-dried particles is responsible for good compressibility and flowability of metformin hydrochloride.

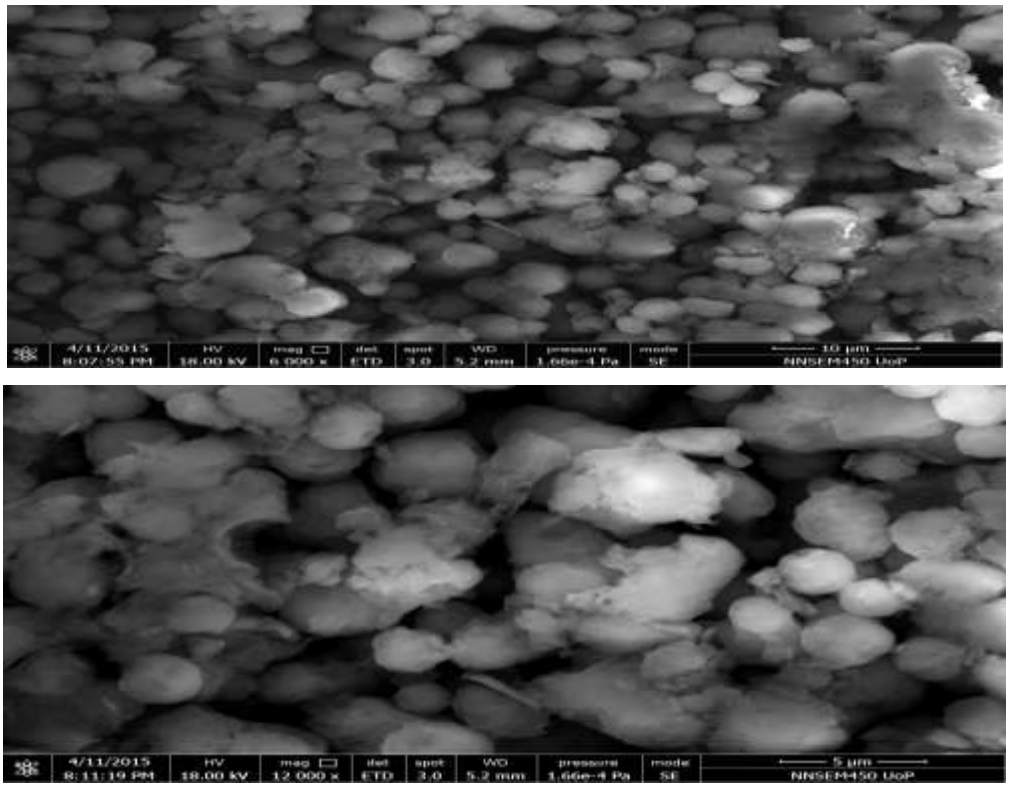

Fig. No. 7: SEM of Metformin HCL and SLS Spray dried powder.

Scanning Electron Microscopy (SEM) was done to reduce the particle size and increase the flow property of Metformin HCL. Particle size was reduced to increase the bioavailability of the drug. After doing SEM it was concluded that the particle size was reduced from the original size of drug. After spray drying the particle size of drug was reduced up to 5µm-10µm. The flow property was also increased.

8.2.: Preformulation Study of Polymers[18,19,20]

1. Appearance and colour

The polymers (Sodium Salicylate, Cyclodextrin, Chitosan) powder was examined for its organoleptic properties like colour and appearance.

Table No. 4 : Colour profile of different polymer.

Sr.No.	Polymer	Colour
1.	Sodium Salicylate	White smooth powder
2.	Cyclodextrin	White crystalline powders
3.	Chitosan	White powders

2. **Solubility:** Solubility of polymers was determined in various solvents like Methanol and Water.

Table No. 5: Solubility profile of different polymer.

Sr.No.	Polymer	Ether	Water
1.	Sodium Salicylate	practically insoluble	Freely soluble
2.	Cyclodextrin	insoluble	Freely soluble
3.	Chitosan	Slightly insoluble	Sparingly soluble

3. Melting point determination

The melting point of the different polymer was determined by open capillary method using melting point apparatus.

Table No. 6: Melting point determination of different polymer.

Sr.No.	Polymer	Melting point
1.	Sodium Salicylate	207.8^{o} C
2.	Cyclodextrin	265.8 ^{o} C
3.	Chitosan	203^{o}C

4. Infrared Spectroscopy[23,24]

The infrared spectra of different polymers were recorded by Shimadzu S 8400 FTIR spectrometer. Samples were prepared by KBr disc method (~2 mg sample in 100 mg KBr) and examined in the transmission mode. Spectrum was measured over a frequency range of 4000–400 cm^{-1}.

4.1 FT-IR spectrum of Sodium Salicylate

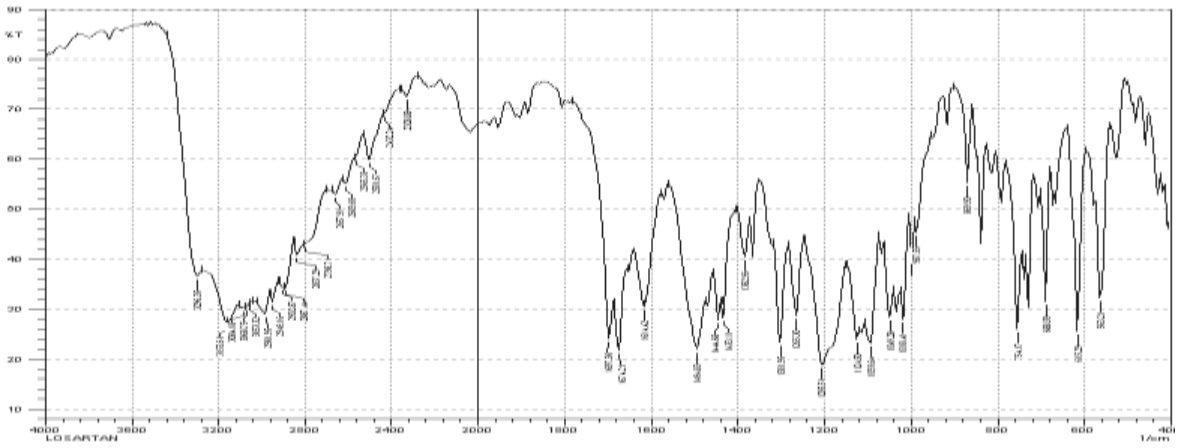

Fig. No. 8: FT-IR spectrum of Sodium Salicylate.

The FT-IR spectra of Sodium Salicylate shows peaks at wave numbers (cm-1) which correspond to the functional groups present in the structure of the Sodium Salicylate. The functional groups determined were similar to the values given in literature.

Table No. 7: FT-IR spectra of Sodium Salicylate.

Sr. No.	Functional groups	Ranges cm $^{-1}$
1.	C=C Stretching	1675
2.	C-H stretching	3250
3.	O-H stretching	3571
4.	C=O stretching	1725

4.2. FT-IR spectrum of β-Cyclodextrin

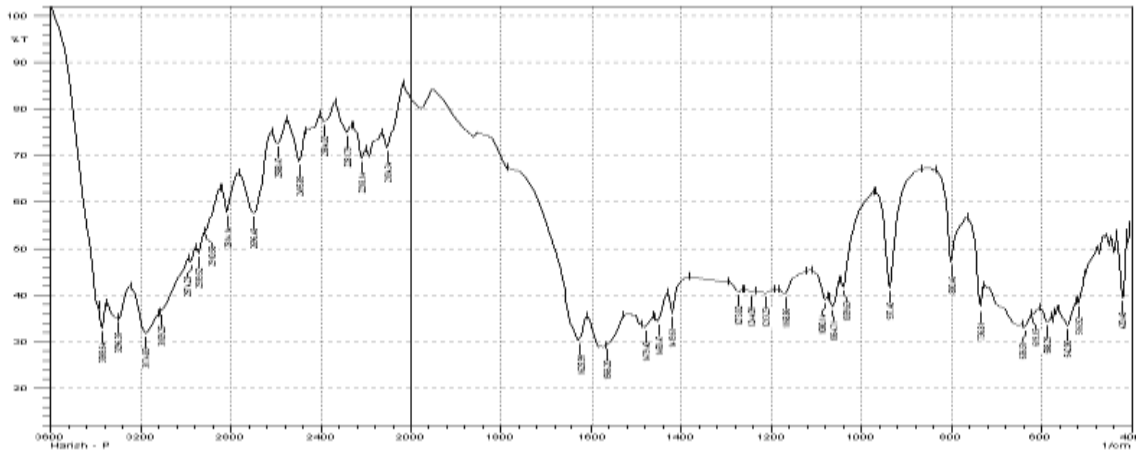

Fig. No. 9: FT-IR spectrum of β-Cyclodextrin.

The FT-IR spectra of β-Cyclodextrin shows peaks at wave numbers (cm-1) which correspond to the functional groups present in the structure of the β-Cyclodextrin. The functional groups determined were similar to the values given in literature.

Table No. 8: FT-IR spectra of β-Cyclodextrin

Sr. No.	Functional groups	Ranges cm $^{-1}$
1.	C-H Stretching	3307
2.	C-H bending	1450
3.	C=C stretching	1641
4.	C-0 stretching	1029
5.	O-H stretching	3441

4.3. FT-IR spectrum of Chitosan

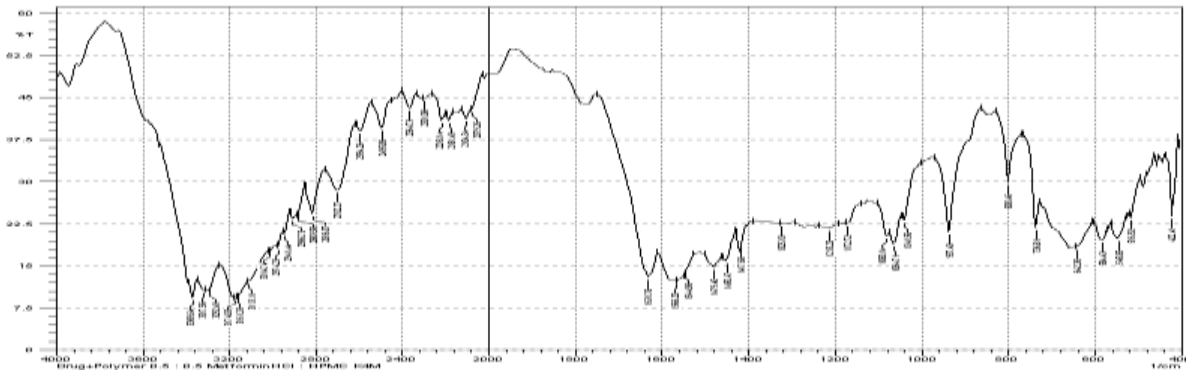

Fig. No. 10: FT-IR spectrum of Chitosan.

The FT-IR spectra of Chitosan shows peaks at wave numbers (cm-1) which correspond to the functional groups present in the structure of the Chitosan. The functional groups determined were similar to the values given in literature.

Table No. 9: FT-IR spectra of Chitosan.

Sr. No.	Functional groups	Ranges cm $^{-1}$
1.	C-H Stretching	2870
2.	O-H Stretching	3250
3.	N-H Stretching	3471

5. Formulation of Tablets

The spray dried powder is used for the formulation. Different permeation enhancer is used to increase the permeation of the drug. Direct Compression method is used for the tablet formulation and punching of the tablet. All the excipient used are shown in the **table no. 10.**

Table No. 10: Formulation table chart

Sr. No.	Ingredients	F - 1	F– 2	F - 3	F – 4	F – 5	F - 6	F – 7	F – 8	F - 9
1.	Metformin HCL + SLS (Spray Dried)	250	250	250	250	250	250	250	250	250
2.	Lactose	140	90	40	140	90	40	140	90	40
3.	**Sodium Salicylate**	**50**	**100**	**150**	-	-	-	-	-	-
4.	**Cyclodextrin**	-	-	-	**50**	**100**	**150**	-	-	-
5.	**Chitosan**	-	-	-	-	-	-	**50**	**100**	**150**
6.	Microcrystalline Cellulose	35	35	35	35	35	35	35	35	35
7.	Aerosil	5	5	5	5	5	5	5	5	5
8.	Crosspovidone	10	10	10	10	10	10	10	10	10
9.	Magnesium Stearate	5	5	5	5	5	5	5	5	5
10.	Talc	5	5	5	5	5	5	5	5	5

6.1. Pre-Compression Parameters[31,32,33]

The Immediate release tablet of Metformin Hydrochloride was evaluated for their pre-compression parameters. Results of all the pre-compression parameters was shown in table No.11.the result revealed that the prepared tablet was complies with the standards of all parameters like, angle of repose, bulk and tapped density, compressibility index, hausner ratio.

6.1.1. Bulk Density and Tapped Density

A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder of Immediate release tablet of Metformin Hydrochloride; such a comparison is often used as an index of the ability of the powder to flow. The bulk density and tapped density was shown in **table No.11**. It complies with the official standards.

6.1.2. Compressibility Index and Hausner ratio

A simple indication of ease with which a material can be induced to flow is given by application of a compressibility index. The value for compressibility index and Hausner ratio was found to be 13.8% and of 1.16, respectively as shown in **table no.11**.It complies with the standards reported in official IP monograph.

6.1.3. Angle of Repose

The angle of repose for formulated blend of Immediate release tablet of Metformin Hydrochloride was carried out and the result were shown in table no. 22. It found to be in the range of $21^{0}80$ showed excellent flow property which confirmed free flowing nature of powder.

Table No. 11: Pre-Compression Parameters.

Sr. No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hauser's Ratio	Angle of repose (^{0})
F-1	0.505±0.010	0.618±0.016	18.28±0.39	1.23±0.01	34.43±0.89
F-2	0.622±0.025	0.787±0.039	20.95±0.75	1.26±0.01	30.73±0.08
F-3	0.603±0.022	0.691±0.030	12.76±0.52	1.14±0.01	31.45±1.04
F-4	0.614±0.008	0.706±0.011	13.02±1.26	1.15±0.02	31.22±0.10
F-5	0.604±0.014	0.745±0.009	18.93±0.92	1.23±0.02	31.42±0.18
F-6	0.446±0.010	0.530±0.014	15.78±0.36	1.19±0.01	23.89±1.09
F-7	0.585±0.011	0.699±0.016	16.30±0.36	1.19±0.01	34.64±0.09
F-8	0.593±0.012	0.694±0.017	14.49±0.27	1.16±0.01	34.93±0.14
F-9	0.638±0.018	0.753±0.013	15.25±1.27	1.18±0.02	28.86±0.12

6.2. Post Compression Parameter[31,32,33]

All the result of post compression parameters was showed in table no.12 .The result of all the parameters revealed that the prepared Immediate release tablet of Metformin Hydrochloride complies with the standards acceptance criteria.

6.2.1. Tablet Dimensions

The thickness and diameter of all the batches of Immediate release tablet of Metformin Hydrochloride was found to be in the range of standards acceptance criteria. As shown in **table no.12** indicating that tablet showed good dimensions.

6.2.2. Hardness

The measured hardness of Immediate release tablet of Metformin Hydrochloride of each optimized batch ranged between 8 to 10.5 kg/cm^2. As shown in table no. 12. The result revealed all the batches showed good mechanical strength this ensures good handling characteristics of all batches.

6.2.3. Friability Test

The friability of all the optimized batches F1 to F9 of Immediate release tablet of Metformin Hydrochloride was in the range as shown in table no. 12 .The % friability was less than 1% in all formulation ensuring that the tablet were mechanically stable. The
result revealed that the prepared Immediate release tablet of Metformin Hydrochloride passes the friability test as per official standards.

6.2.4. Disintegration Test:

The Disintegration Test for all batches from F1 to F9 of Immediate release tablet of Metformin Hydrochloride is shown in **table No. 12**. It complies with official specifications reported in Indian Pharmacopoeia.

6.2.5. Determination of Drug Contents

The percentage of drug content for all batches from F1 to F9 of Immediate release tablet of Metformin Hydrochloride was found to 96 % of Metformin Hydrochloride as shown in **table No. 12** It complies with official specifications reported in Indian Pharmacopoeia.

Table No. 12: Post -Compression Parameters.

Sr.no	Thickness (mm)	Diameter (cm)	Hardness (kg/cm2)	Friability (%)	Disint. Time in min.	Drug Content (%)
F-1	10.11	0.52±0.09	10	0.87	10.40±0.09	91 %
F-2	10.12	0.51±0.14	9	0.84	11.07±0.06	91 %
F-3	10	0.55±0.18	10.5	0.47	12.08±0.08	92 %
F-4	10.12	0.52±0.22	10	0.27	10.10±0.05	95 %
F-5	10.13	0.52±0.22	9	0.24	12.67±0.29	95 %
F-6	10	0.51±0.10	10	0.23	13.38±0.08	96 %
F-7	10	0.52±0.21	9	0.24	12.18±0.03	92 %
F-8	10.11	0.50±0.36	8	0.21	15.85±0.30	92 %
F-9	10.12	0.53±0.22	10	0.19	14.07±0.03	93 %

6.2.6. FTIR Studies[23,24]

FTIR studies were performed using IR spectrophotometer. FTIR techniques have been used here to study the physical and chemical interaction between Metformin Hydrochloride and the polymers used The IR spectrum and IR interpretation of optimized F-6 batch shows in figure no.15. The observed spectrum represents drug to polymer super-imposed pattern with their significant functional group at specific wavelength. Spectrum represent significant functional group from drug to polymer, no new additional peak formation was observed indicated that there was no any chemical interaction between drug and polymers only the physical interaction was takes place in terms of hydrogen bonding. The peaks obtained in the spectra's of each polymer correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

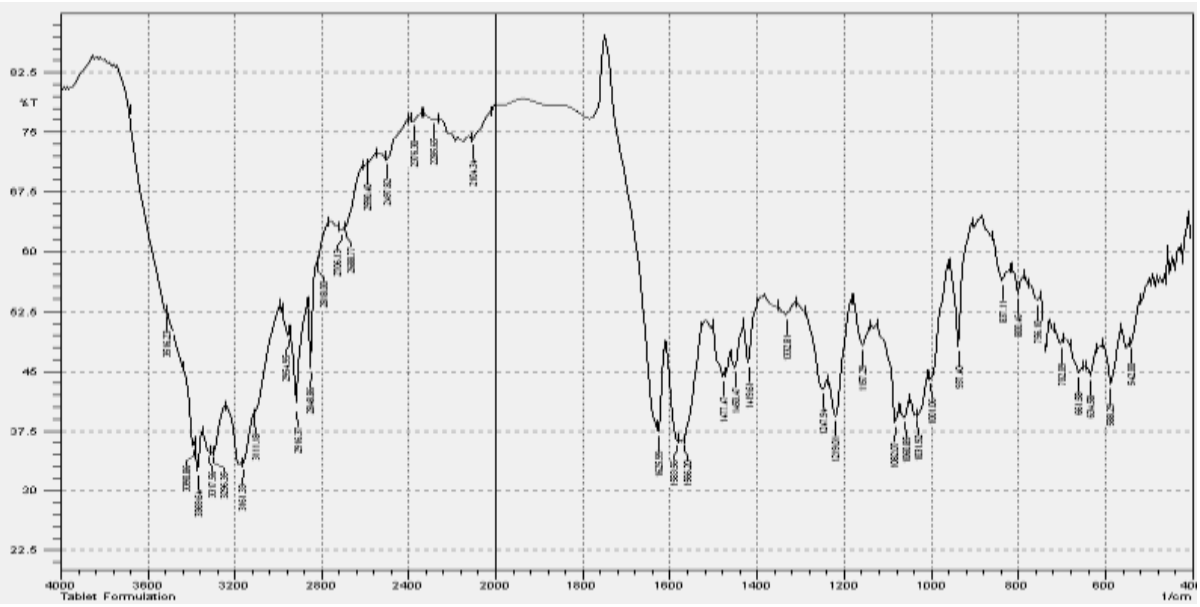

Fig. No. 13: FT-IR spectrum of optimized (F-6) formulation.

6.2.7. Differential Scanning Calorimetry (DSC) Study for Optimized Batch[25]

The differential scanning calorimetry for optimized F-6 batch was showed in figure no. 14. The sharp endothermic peak at 224 ^{0}C, 152^{0}C, 207^{0}C and 244.18^{0}C indicate that drug polymorph melts and present in more amorphous polymeric form respectively, which help to exhibit more solubility of drug polymorph.

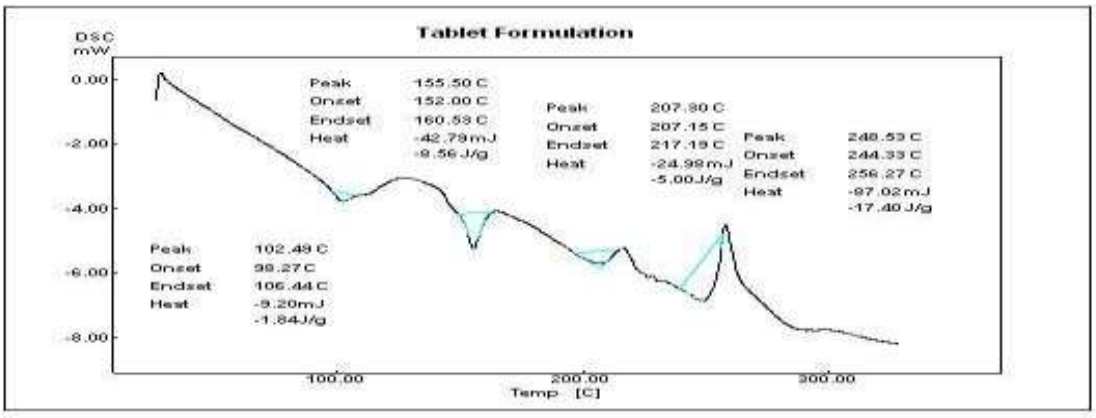

Fig. No. 14: DSC thermogram of optimized (F-6) formulation.

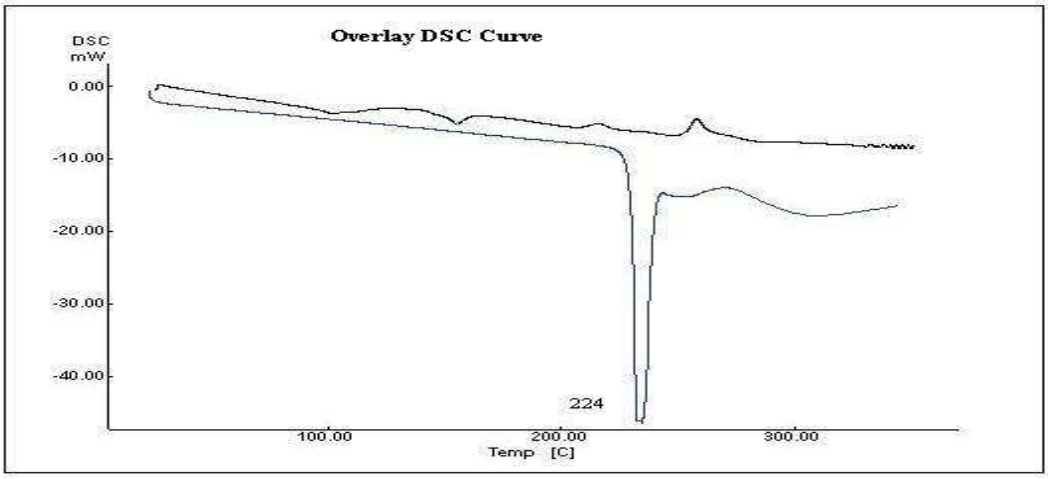

Fig. No. 15: DSC overlay thermogram.

6.3. In vitro drug release studies[35]

Dissolution studies on all the optimized batches of Immediate release tablet of Metformin Hydrochloride were carried out using USP type –II (rotating paddle) dissolution apparatus **(Electrolab TDT 08L).** The result obtained in in-vitro release studies were plotted in four models of data treatment as follows.

1. Zero order rate kinetic
2. First order rate kinetic
3. Higuchi-matrix

4. Korsmeyer-Peppas

The in-vitro release data obtained for all batches was shown in figure no. 18. The cumulative percent drug release after 80 min. is recorded and it is observed. The results obtained shows that the height drug release 99.81% for F-6 batch. From the in-vitro release studies it was found that there was an increase in drug release. From the obtained result it was concluded that the drug release from formulation increased with increased in polymer concentration.

Table No. 13: In-Vitro % release of all the batches.

Time in min.	Batch F-1	Batch F-2	Batch F-3	Batch F-4	Batch F-5	Batch F-6	Batch F-7	Batch F-8	Batch F-9
0	0	0	0	0	0	0	0	0	0
5	11.28	9.92	12.34	9.73	14.29	8.67	7.29	8.73	9.37
10	18.995	10.326	17.711	11.653	17.23	11.423	10.829	10.853	12.585
15	33.705	19.717	33.332	21.065	26.413	17.122	19.538	18.811	19.703
20	47.103	30.102	41.785	29.675	37.881	28.593	25.3	27.098	36.887
30	55.016	35.019	51.549	37.699	46.013	39.083	34.249	35.722	44.371
40	67.889	48.038	63.76	48.792	57.028	52.613	49.451	47.267	54.933
45	81.668	57.686	81.502	61.03	74.535	61.501	55.943	55.683	64.054
50	87.861	65.156	86.984	67.378	81.125	83.482	64.568	62.461	72.052
60	93.975	73.539	92.003	75.042	88.45	99.819	68.437	69.664	85.297
70	96.129	87.926	99.493	85.781	91.32		86.601	86.601	99.217
80	99.138	98.518		98.565	98.71		98.197	98.081	

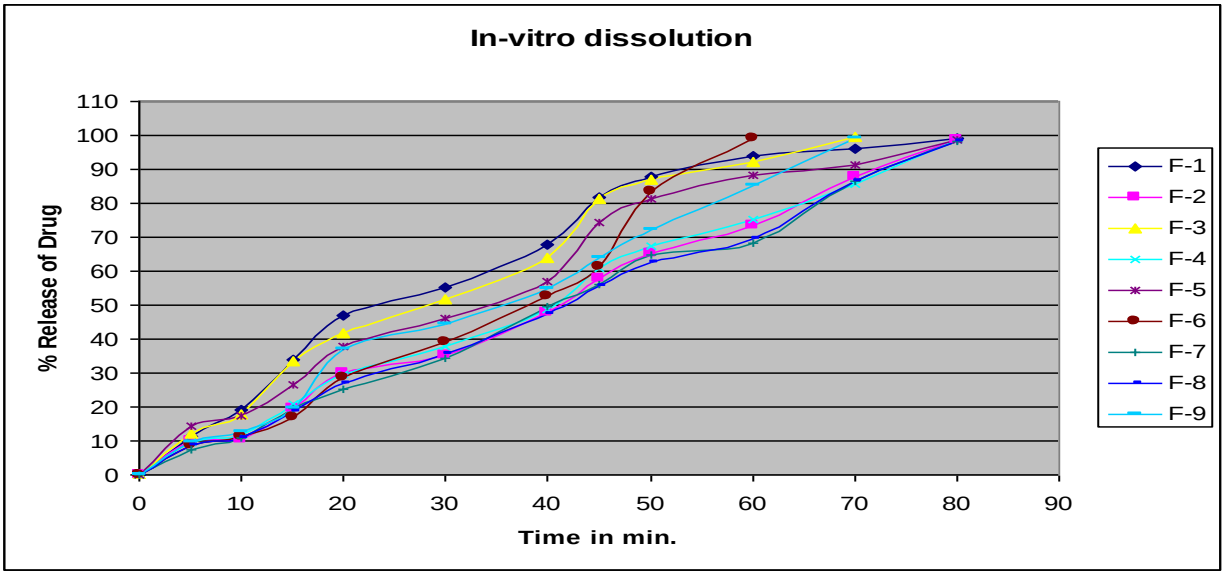

Fig. No. 16: In-Vitro % release of profile of all the batches.

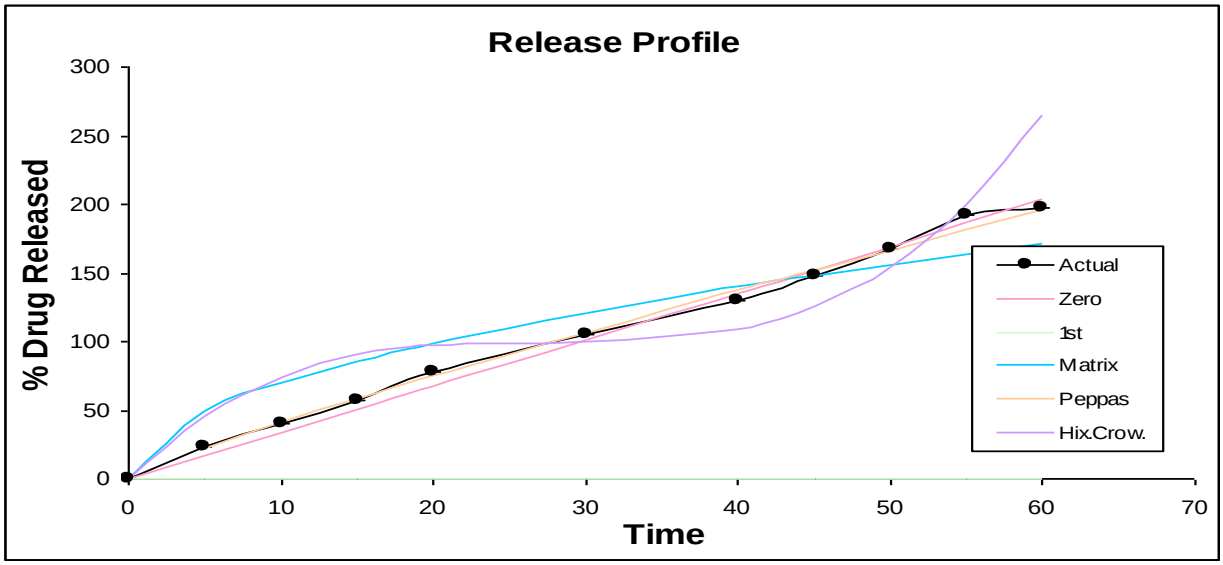

Fig. No. 17: Best fit model is Korsmeyer – Peppas

Drug Release Mechanism

The in vitro release data was analyzed using various kinetic models like Zero order, First order, Higuchi matrix and Korsmeyer-Peppas in order to find out the mechanism of drug release. These values were compared with each other for model and drug equation as shown in figure no. 19 .The Korsmeyer-Peppas model fits the data to following general equation.

$$M_t/M_\infty = kt^n$$

Where, M_t/M_∞ is the fraction of the drug release at time t and k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms and is calculated from the slop of the plot of fraction of drug released Vs log of time.

6.4. In vivo drug release studies[13, 14]

The in-vivo drug release was studied using everted sac method.

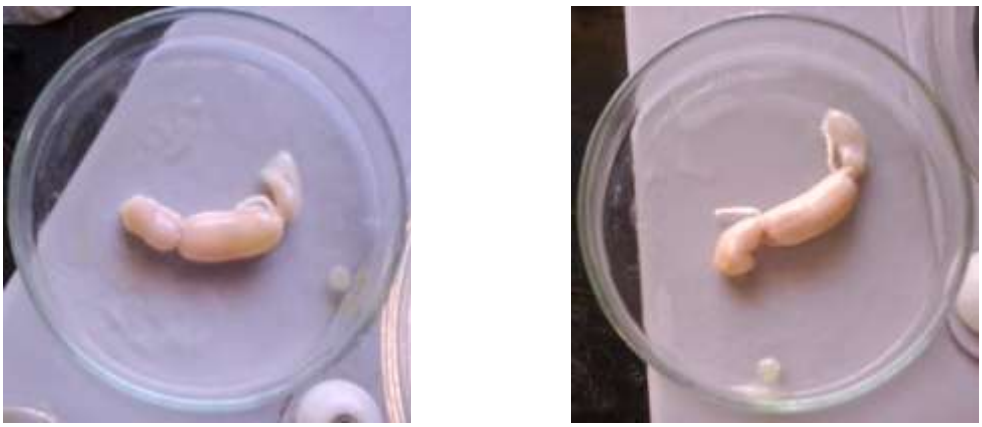

Fig. No. 18: Everted Sac In Vivo Dissolution Study.

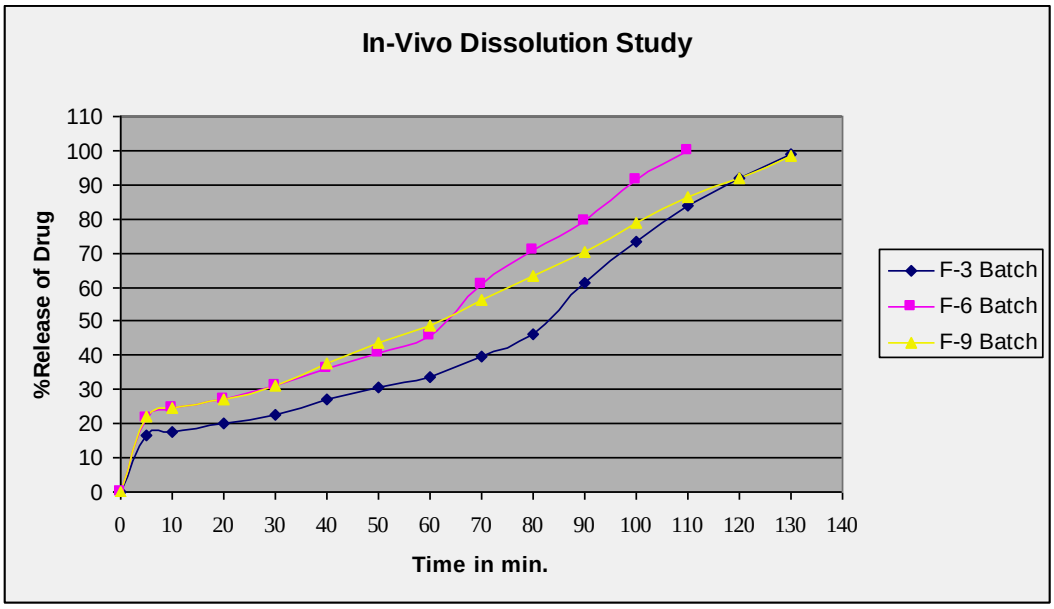

Fig. No. 19: In-Vivo drug release of optimized batches.

The dissolution study was compared with the in-vitro drug release profile. The three optimized batch was taken for the in-vivo study. Among this the Cyclodextrin batch was the best which shows the more permeation of the drug then other two permeation enhancers.

6.5.Stability Studies[36]

The stability studies were carried out for Immediate release tablet of Metformin Hydrochloride at elevated temperature 40°C and 75% RH for 3 months on the optimized batches and result reported in table no. . Tablets were observed for any change in colour, odour and drug content The stability result was indicated that the optimized batches was stable for 3 months.

6.5.1. Physical appearance

a) Colour : Unchanged

b) Odour : Unchanged

6.5.2. Drug content

Table No. 14: Drug content for stability study.

Sr. No.	Drug content before stability study	Drug content after 1 month	Drug content after 2 month	Drug content after 3 month
1.	98.61±1.92	97.22±1.03	97.12±1.32	96.48+1.67

CONCLUSION

- In this work, an antidiabetic tablet containing natural permeation enhancer was formulated which enhanced the absorption of poorly absorbable antidiabetic drug from intestine.
- The absorption of Metformin HCL in humans is very low according to Biopharmaceutical Classification System.
- The absorption studies were conducted for poorly absorbable antidiabetic drug metformin hydrochloride with different permeation enhancer.
- The absorbed drug was determined by using U.V Visible Spectrophotometer at 234nm.
- After analyzing the results it was concluded that Cyclodextrin has best absorption enhancing activity of metformin hydrochloride then the other two permeation enhancer.
- Cyclodextrin help to reduce dose of metformin hydrochloride in tablet dosage form.
- Purity of drug was evaluated by FTIR and DSC study.
- Drug excipient compatibility study was evaluated by FTIR.
- For optimizing the dose of metformin hydrochloride, different batches of tablets (F1 to F9) was formulated by direct compression method with different concentration of permeation enhancer.
- Pre-compression and Post-compression study was done for the tablet formulation and results was recorded.
- In-Vitro everted sac method using chicken intestine was selected for the absorption studies.
- Hence, the result showed that the use of permeation enhancer like cyclodextrin, enhance the permeation of drug.

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