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PREPARATION AND *IN-VITRO* EVALUATION OF IMMEDIATE RELEASE TABLETS OF CHLORPROPAMIDE

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Abstract:

The aim of the present study is to develop and evaluate the immediate release tablet of Chlorpropamide by direct compression method. The Superdisintegrant Primojel, Ac-Di-Sol and Polyplasdone XL10 were used for immediate release of drug from tablet. The prepared tablets were evaluated for all pre-compression parameters and post-compression parameters. The drug excipients interaction was investigated by FTIR. All formulation showed compliances with Pharmacopoeial standards. The study reveals that formulations prepared by direct compression F3 exhibit highest dissolution using Crospovidone showed faster drug release 98.01% over the period of 45min while disintegration time of the tablet was showed 25sec comparison to other formulations of Chlorpropamide.

Key words: *Chlorpropamide, superdisintegrant and Immediate release tablet.*

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INTRODUCTION:

Oral route is the most convenient and extensively used for drug administration. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance suitable for industrial production, improved stability and bioavailability. The concept of immediate release tablets emerged from the desire to provide patient with more conventional means of taking their medication when emergency treatment is required. Recently, immediate release tablets have gained prominence of being new drug delivery systems. The oral route of administration has so far received the maximum attention with respect to research on physiological and drug constraints as well as design and testing of product, Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. Several orally disintegrating tablet (ODT) technologies based on direct compression. In pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation is at least 70% (preferably 80%) of active ingredient within 4 hours, such as within 3 hours, preferably 2 hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes) of administration. In Formulation of immediate release the commonly Superdisintegrants used are Croscarmellose, sodium, Sodium Starch glycolate and Crospovidone.

Oral route of administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems does not need sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. There is requirement for new oral drug delivery system because of poor patient acceptance for invasive methods, requirement for investigation of new market for drugs and combined with high cost of disease management. Developing new drug delivery techniques and that utilizing in product development is critical for pharma companies to survive this century.

The term ‘immediate release’ pharmaceutical formulation is the formulation in which the rate of release of drug and/or the absorption of drug from the formulation, is neither appreciably, nor intentionally, retarded by galenic manipulations. Immediate release dosage form is those which break down quickly and get dissolved to release the medicaments. In the present case, immediate release may be provided of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not delay, to an appreciable extent, the rate of drug release and/or absorption.

Immediate release drug delivery is suitable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life. But main requirement for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat undesirable imperfection or disease.

Pharmacokinetics:

It is the study of absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Pharmacodynamic:

- Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ.
- Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
- Decreased sensitivity of the CVS to α-adrenergic agonist and antagonist.
- Immunity is less and taken into consideration while administered antibiotics.
- Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline
- shows increased sensitivity to barbiturates.
- Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.
- Research workers have clinically evaluated drug combination for various classes cardiovascular

agents, diuretics, anti-hypertensive etc. for immediate release dosage forms. The combination choice depends on disease state of the patient.

MATERIALS AND METHODS:

Chlorpropamide Provided by SURA LABS, Dilsukhnagar, Hyderabad, Primojel from Merck Specialities Pvt Ltd, Ac-Di-Sol from Merck Specialities Pvt Ltd, Polyplasdone XL10 from Merck Specialities Pvt Ltd, Beta-Cyclodextrin from Merck Specialities Pvt Ltd, MCC from Merck Specialities Pvt Ltd, Aspartame from Merck Specialities Pvt Ltd, Mg stearate from Merck Specialities Pvt Ltd, Talc from Merck Specialities Pvt Ltd

Characterization of Chlorpropamide:

Organoleptic properties:

Take a small quantity of sample and spread it on the white paper and examine it visually for color, odour and texture.

Determination of Chlorpropamide Melting point:

The melting point of Chlorpropamide was determined by capillary tube method according to the USP. A sufficient quantity of Chlorpropamide powder was introduced into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Chlorpropamide in the tube passed into liquid phase**.**

Buffer Preparation:

Preparation of 0.2M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm sodium hydroxide pellets were dissolved 1000ml of distilled water and mixed.

Preparation of pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium Dihydrogen ortho phosphate and 112.5 ml 0.2M NaOH was taken into the 1000ml volumetric flask. Volume was made up to 1000ml with distilled water.

Analytical method development for Chlorpropamide:

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 240 nm. Hence all further investigation was carried out at the same wavelength.

b) Preparation of Standard graph in pH 6.8 phosphate buffer

100 mg of Chlorpropamide was dissolved in 100ml of Phosphate buffer of pH 6.8., form primary stock 10ml was transferred to another volumetric flask made up to 100ml with Phosphate buffer of pH 6.8, from this secondary stock was taken separately and made up to 10 ml with Phosphate buffer of pH 6.8, to produce 2, 4, 6, 8 and 10µg/ml respectively. The absorbance was measured at 240 nm by using a UV spectrophotometer.

Formulation Development:

Drug and different concentrations for super Disintegrates and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes. The obtained blend was lubricated with Magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes. The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Table 1: Formulation of Immediate Release tablets

Total weight of tablets = 300 mg

RESULT AND DISCUSSION:

INGREDIENTS	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlorpropamide	100	100	100	100	100	100	100	100	100
Primojel	40	80	120	-	-	-	-	-	-
Ac-Di-Sol	-	-	-	40	80	120	-	-	-
Polyplasdone XL10	-	-	-	-	-	-	40	80	120
Beta-Cyclodextrin	10	20	30	10	20	30	10	20	30
MCC	122	72	22	122	72	22	122	72	22
Aspartame	15	15	15	15	15	15	15	15	15
Mg stearate	7	7	7	7	7	7	7	7	7
Talc	6	6	6	6	6	6	6	6	6
Total Weight of Tablet (mg)	300	300	300	300	300	300	300	300	300

Organoleptic properties

Table 2: Organoleptic properties

S NO.	Properties	Reported results	Observed results
1	State	Solid	Solid
2	Colour	White	White
3	Odour	Odourless	Odourless
4	Melting point	129.2-129.8	129.5

Determination of λ_{max}:

The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 240nm.

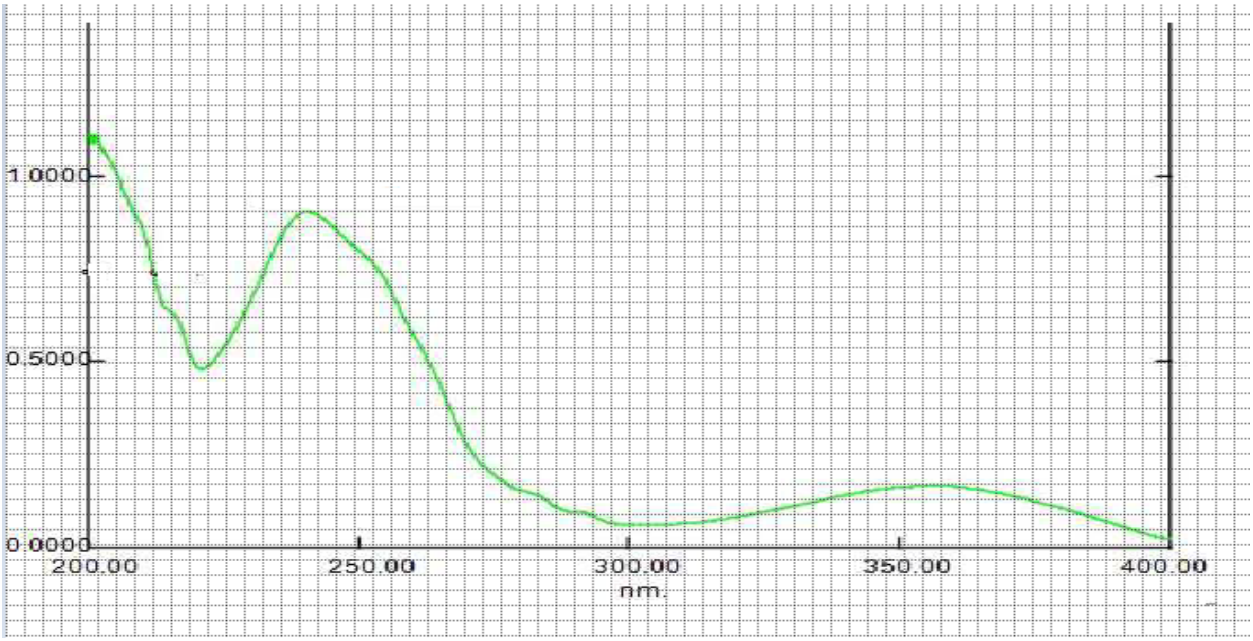

Fig 1: Spectra for Chlorpropamide wavelength optimization

Calibration curve of Chlorpropamide:

The standard curve of Chlorpropamide was obtained and good correlation was obtained with R^2 value of 0.999, the medium selected was pH 6.8 phosphate buffer.

Table 3: Standard graph values of Chlorpropamide at 240 nm in pH 6.8 phosphate buffer

Concentrations (µg/ml)	Absorbance
0	0
2	0.119
4	0.238
6	0.347
8	0.461
10	0.574

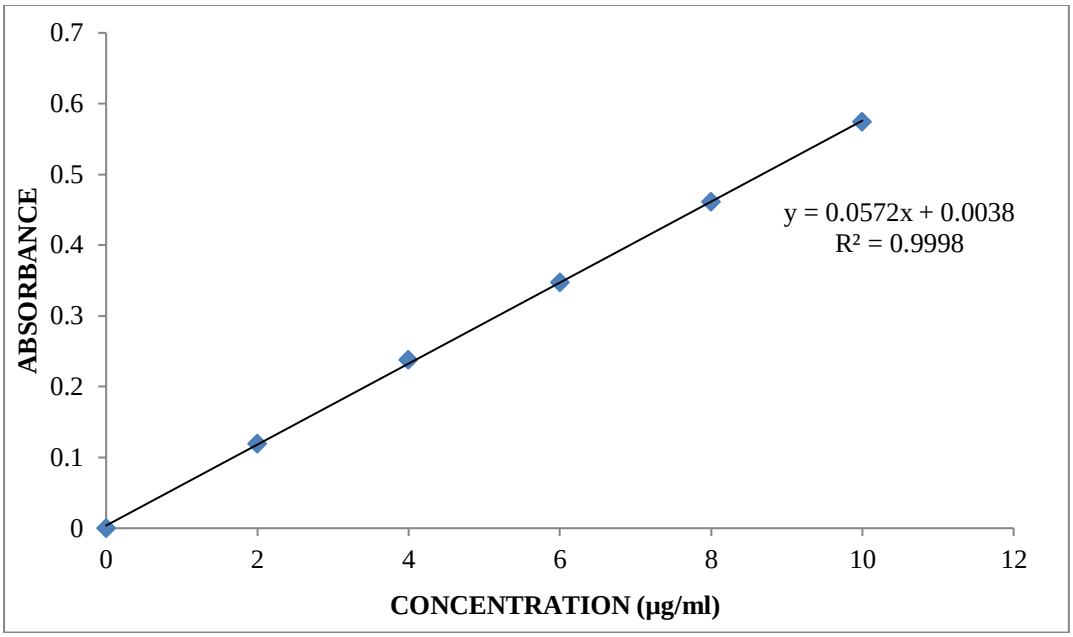

Fig 2: Standard curve of Chlorpropamide

Evaluation:

Characterization of Precompression blend:

The Precompression blend of Chlorpropamide was characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 35.23º, Carr's index values were less than 20.01 for the Precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.26 for all batches indicating good flow properties.

Table 4: Physical properties of Precompression blend

Formulation code	Angle of repose (Ɵ)	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	35.13±0.032	0.4236±0.0026	0.4854±0.0018	12.73±0.0494	1.14±0.0014
F2	35.15±0.041	0.4230±0.0020	0.4766±0.0033	11.23±0.1272	1.12±0.0035
F3	29.24±0.008	0.4127±0.0180	0.4821±0.0029	14.36±0.7566	1.16±0.0000
F4	27.47±0.027	0.4227±0.0038	0.5231±0.0253	19.19±0.0565	1.23±0.0071
F5	35.12±0.019	0.3823±0.0032	0.4852±0.0044	20.01±0.0848	1.26±0.0000
F6	34.99±0.003	0.3910±0.0014	0.4650±0.0036	15.90±0.3040	1.16±0.0070
F7	33.86±0.002	0.2896±0.0014	0.3449±0.0013	16.04±0.3676	1.18±0.0424
F8	35.23±0.001	0.3100±0.0035	0.3655±0.0031	15.19±0.2969	1.17±0.0070
F9	32.61±0.001	0.3925±0.0026	0.4614±0.0028	14.93±0.9545	1.16±0.0070

All the values represent n=3

Evaluation of tablets:

Physical evaluation of Chlorpropamide immediate release tablets:

The results of the weight variation, hardness, thickness, friability and drug content of tablets are given in table 10.3. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit. The hardness of the tablets ranged from 4.0 – 4.9 kg/cm^2 and the friability values were < than 0.61 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 3.15- 3.95 mm. All the formulations satisfied the content of the drug as they contained 96.28-99.35 % of Chlorpropamide and good uniformity in drug content was observed. Thus all physical attributes of the prepared tablets were found to be practically within control limits.

Table 5: Physical evaluation of Chlorpropamide

Formulation code	Weight variation (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content Uniformity (%)	Disintegration Time (Sec)
F1	296.21	3.69	4.2	0.36	98.16	43
F2	298.80	3.48	4.9	0.24	97.62	36
F3	295.16	3.15	4.6	0.59	99.35	25
F4	299.60	3.75	4.1	0.37	96.28	51
F5	296.21	3.61	4.7	0.49	97.19	46
F6	298.52	3.95	4.3	0.36	99.25	40
F7	296.79	3.47	4.2	0.61	99.61	45
F8	298.31	3.64	4.0	0.48	98.18	38
F9	297.10	3.18	4.8	0.57	97.29	31

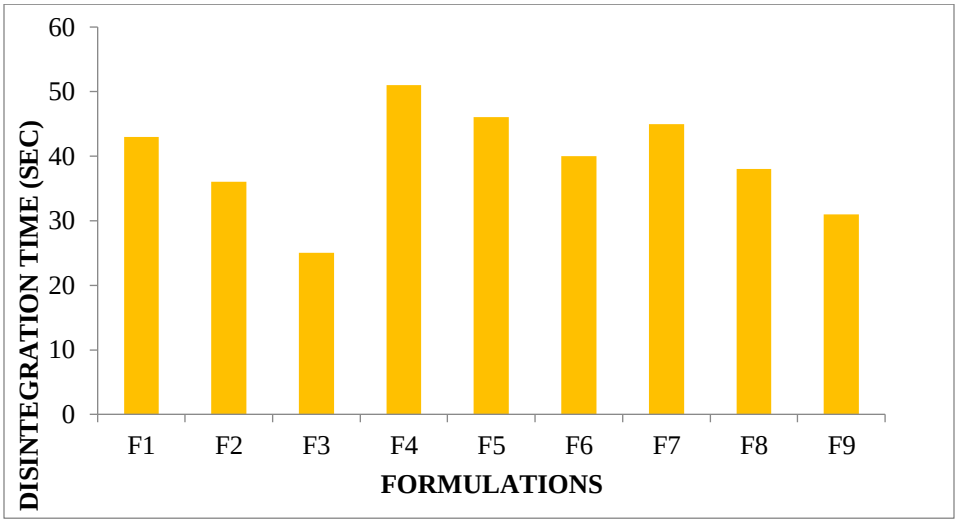

Figure 3: Disintegration Test (Sec)

***In vitro* release studies:**

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 900 ml of pH 6.8 phosphate buffer at 75 rpm at a temperature of 37±0.5˚C. Samples of 5 ml were collected at different time intervals up to 1 hr and has analyzed after appropriate dilution by using UV spectrophotometer at 240 nm.

Table 6: *In vitro* dissolution data for formulation F1-F9

TIME (MIN)	% OF DRUG RELEASE								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
5	14.37	17.33	40.18	10.27	16.18	19.13	12.36	16.34	20.35
10	25.39	29.57	55.68	22.95	29.32	35.95	25.48	29.47	37.22
15	38.37	42.36	62.15	35.89	37.25	48.66	38.99	41.23	49.63
20	47.69	58.75	75.78	46.77	50.87	64.29	46.62	59.65	55.77
25	54.76	66.33	83.84	54.83	65.83	73.85	59.75	65.74	71.32
30	69.54	78.18	97.62	62.16	71.45	81.58	72.31	73.18	83.17
45	83.58	89.65	98.01	71.28	86.73	92.56	81.36	85.62	95.48

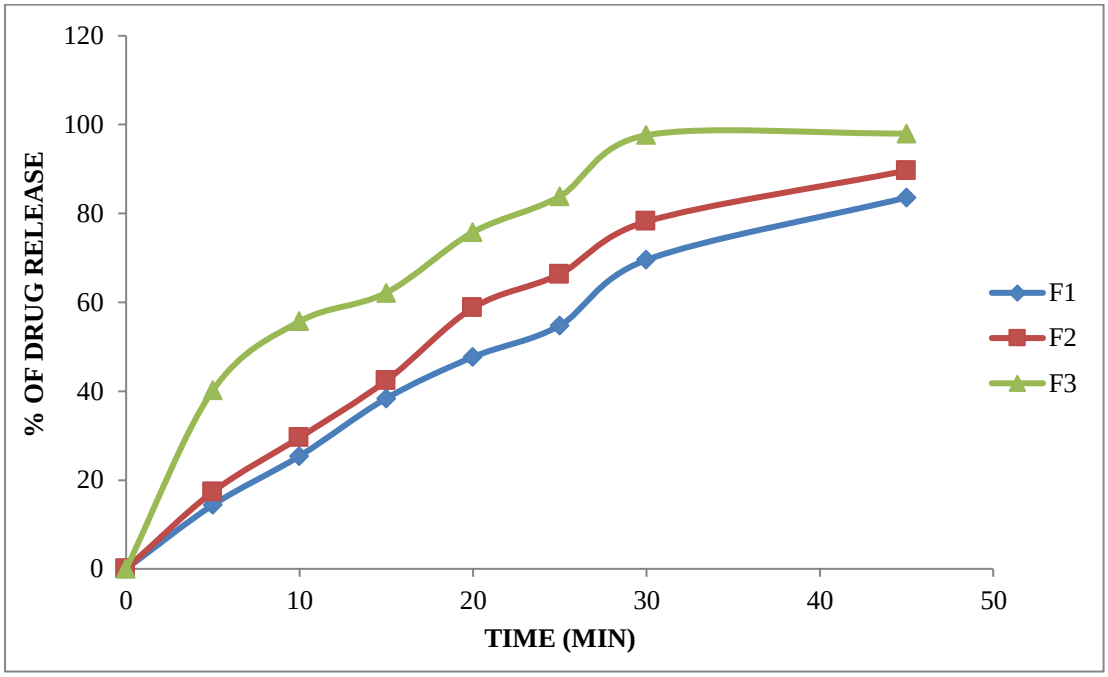

Fig 4: *In vitro* dissolution data for formulation F1-F3

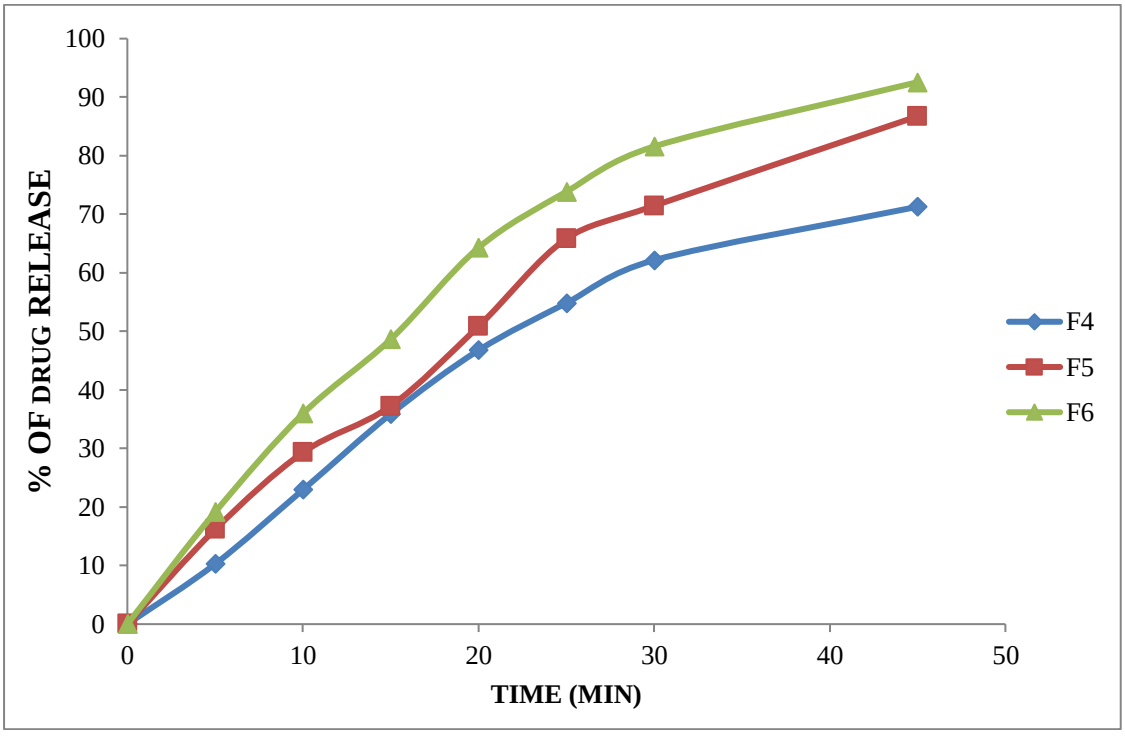

Fig 5: *In vitro* dissolution data for formulations F4-F6

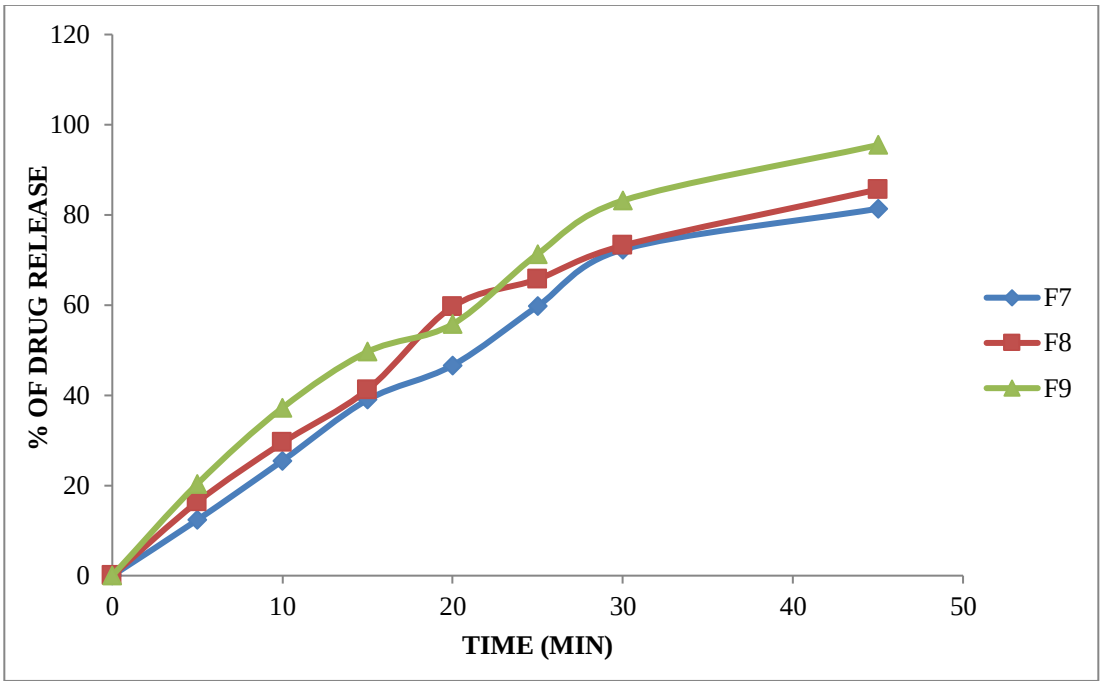

Fig 6: *In vitro* dissolution data for formulations F7-F9

From the table it was evident that the formulation prepared with Primojel were showed good drug release i.e., F3 formulation (97.01%) in higher concentration of blend i.e. 120 mg. Formulations prepared with Ac-Di-Sol showed good drug release i.e., 92.56% (F6 formulation) in 120 mg concentration. When increase in the concentration of Primojel drug release increased. Formulations prepared with Polyplasdone XL10 showed maximum drug release i.e., 95.48% (F9 formulation) at 45 min in 120 mg of blend.

Among all formulations F3 considered as optimized formulation which showed maximum drug release at 45 min i.e., 98.01%. Primojel showed good release when compared to Ac-Di-Sol and Polyplasdone XL10. Finally concluded that F3 formulation contains Primojel was optimized formulation.

The formulations prepared with Beta-Cyclodextrin to increase the solubility, When the Concentration of Beta-Cyclodextrin was increased drug release also increased. The present work involves the formulation development, optimization and *in-vitro* evaluation of immediate release tablets by direct compression technique. Since Chlorpropamide is BCS Class-II drug, direct compression technique was opted to increase its solubility and dissolution rate.

Table 7: Release Kinetics:

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
40.18	5	2.236	1.604	0.699	1.777	8.036	0.0249	-0.396	59.82	4.642	3.911	0.731
55.68	10	3.162	1.746	1.000	1.647	5.568	0.0180	-0.254	44.32	4.642	3.539	1.103
62.15	15	3.873	1.793	1.176	1.578	4.143	0.0161	-0.207	37.85	4.642	3.358	1.284
75.78	20	4.472	1.880	1.301	1.384	3.789	0.0132	-0.120	24.22	4.642	2.893	1.748
83.84	25	5.000	1.923	1.398	1.208	3.354	0.0119	-0.077	16.16	4.642	2.528	2.113
97.62	30	5.477	1.990	1.477	0.377	3.254	0.0102	-0.010	2.38	4.642	1.335	3.306
98.01	45	6.708	1.991	1.653	0.299	2.178	0.0102	-0.009	1.99	4.642	1.258	3.384

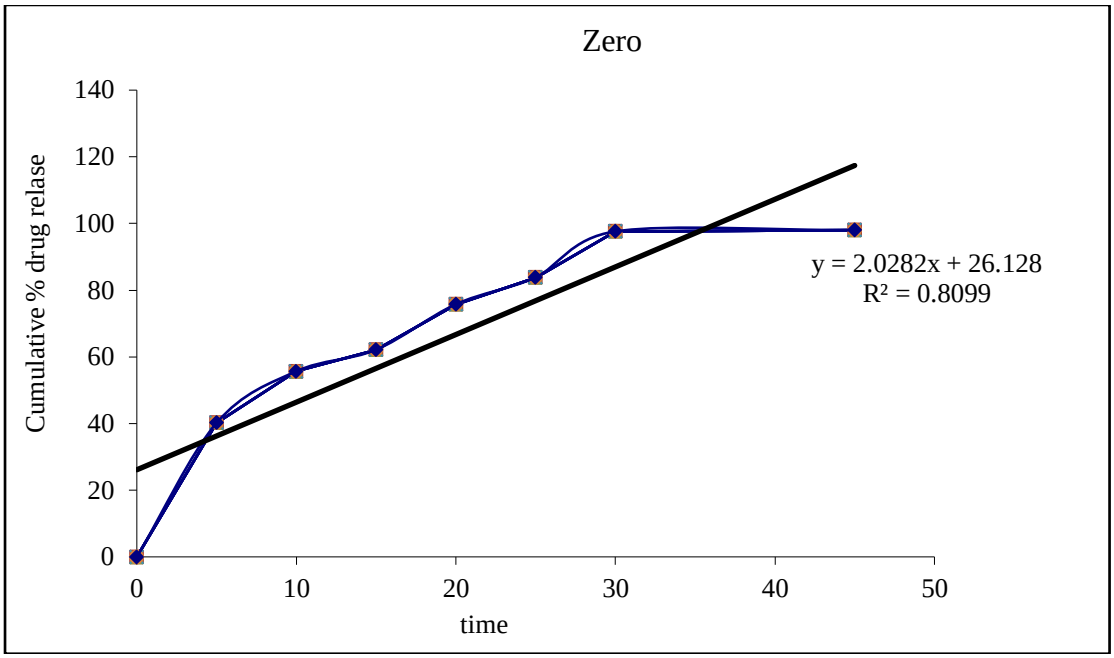

Figure 7: Zero order release kinetics graph

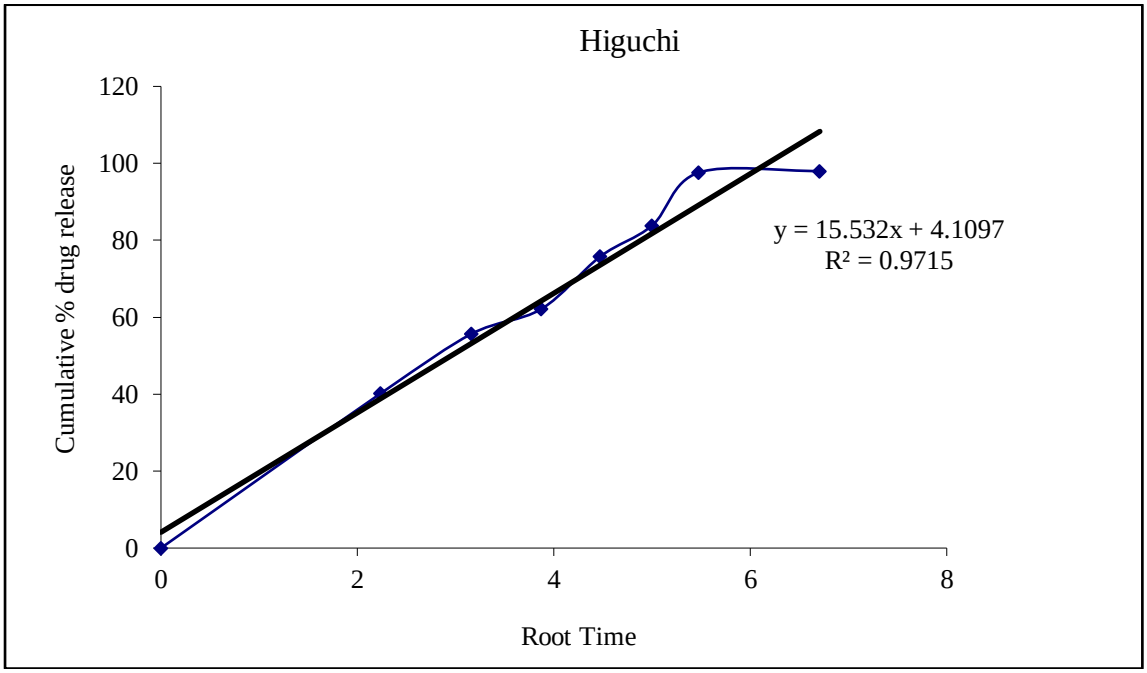

Figure 8: Higuchi release kinetics graph

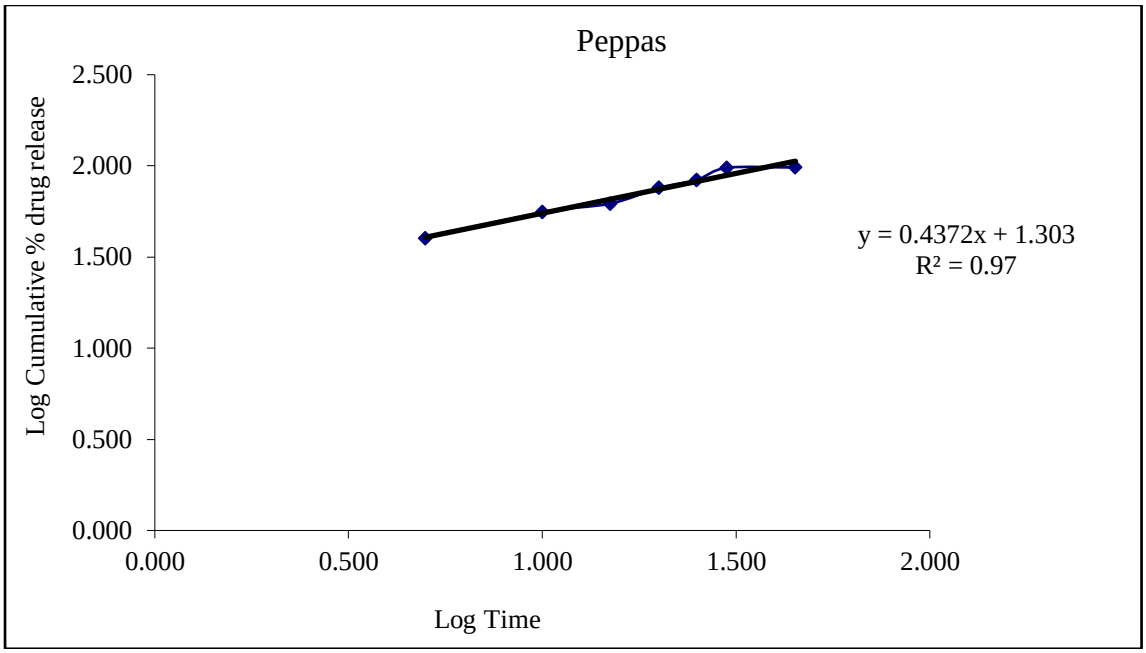

Figure 9 : Peppas release kinetics graph

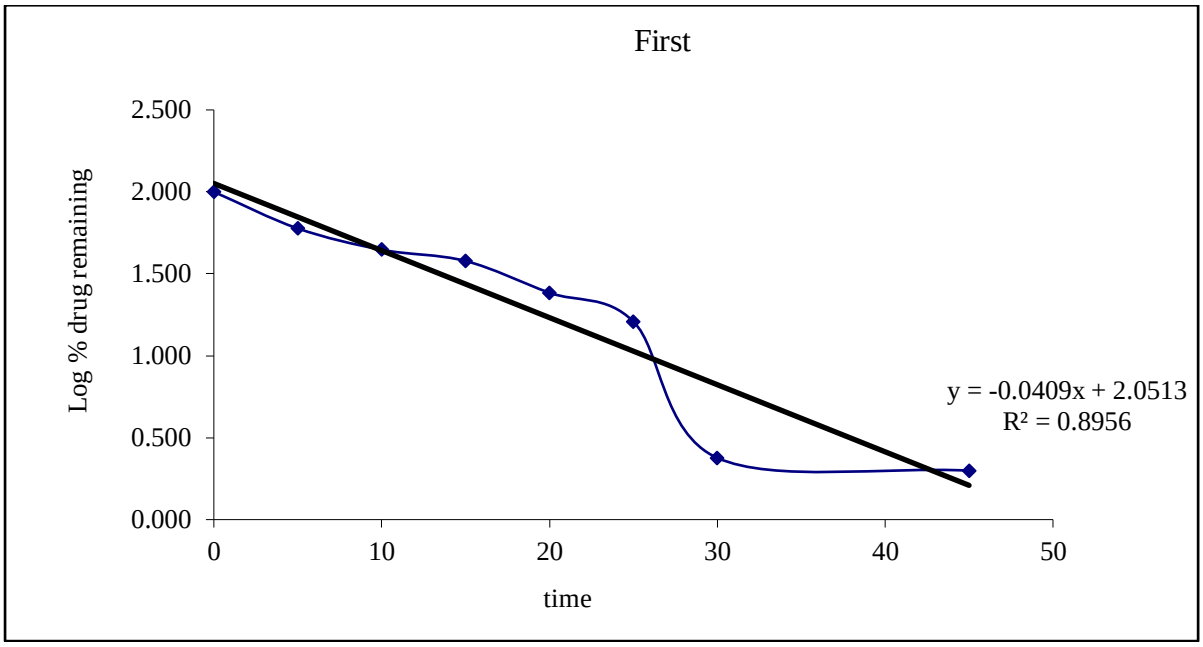

Figure 10: First order release kinetics graph

Optimised formulation F3 was kept for release kinetic studies. From the above graphs it was evident that the formulation F3 was followed **Higuchi release** kinetics mechanism.

Drug-Excipient compatibility studies by FTIR studies:
Chlorpropamide was mixed with various proportions of excipients showed no colour change at the end of two months, providing no drug–Excipient interactions.

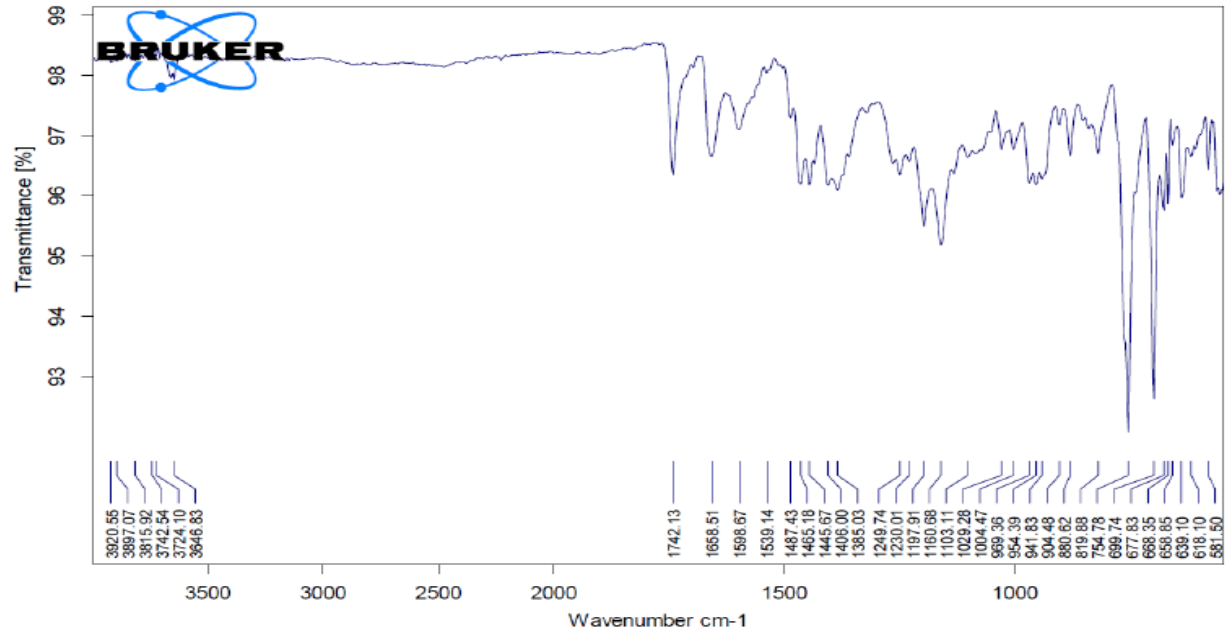

Fig 11: FTIR spectra of pure drug

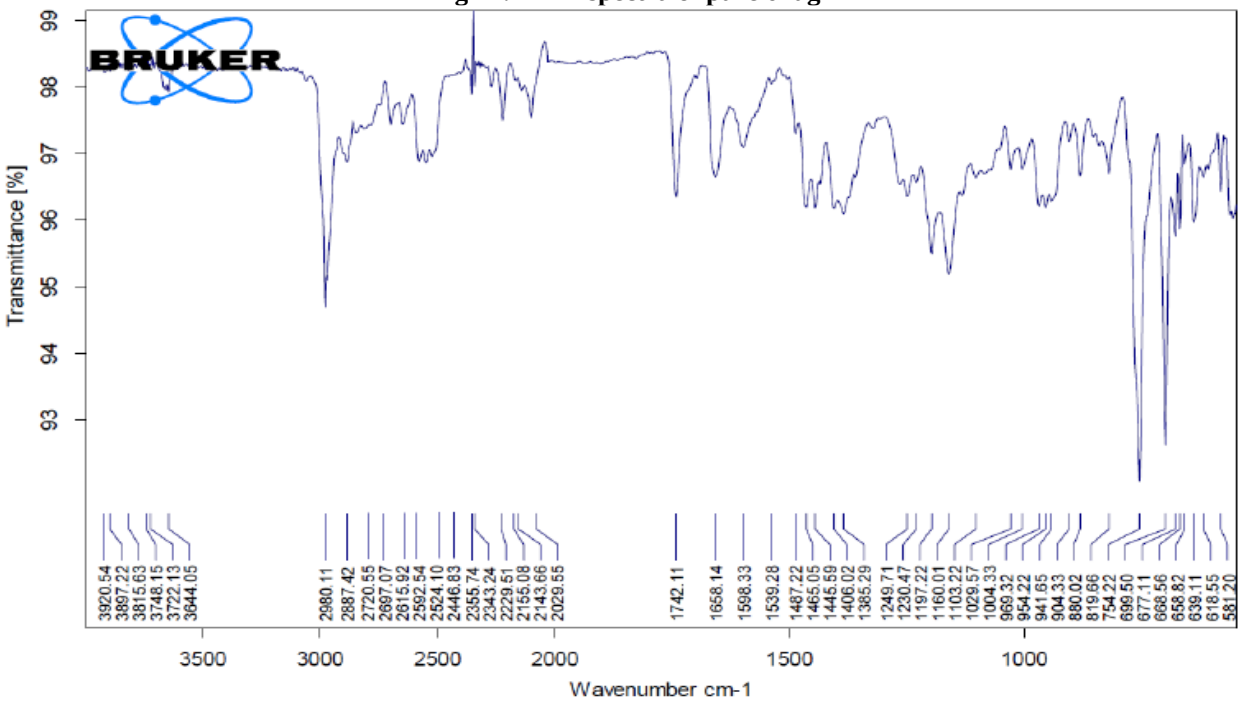

Fig 12: FTIR spectra of optimized formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Chlorpropamide and excipients used in the preparation of different Chlorpropamide Immediate Release formulations. Therefore the drug and excipients are compatible to form stable. Formulations under study, The FTIR spectra of Chlorpropamide and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

Table 8 : Peaks characterization for pure Chlorpropamide

Functional group	Reference wave number (cm−1)	Obtained wave number (cm−1)
C=O (carbonyl)	1656-1715	1658.51
-C=C-Aromatic	1450-1650	1406.00-1598.67
Amide	3675.36	3646.83

Table 9: Peaks characterization for Optimized formulation Chlorpropamide

Functional group	Reference wave number (cm−1)	Obtained wave number (cm−1)
C=O (carbonyl)	1656-1715	1658.14-1742.11
-C=C-Aromatic	1450-1650	1406-02-1598.22
Amide	3675.36	3644.05

CONCLUSION:

The present study was under taken to formulate and evaluate the immediate release tablets of Chlorpropamide by using direct compression technique with various disintegrants. The study involves pre-formulation of drug and excipients, formulation, and evaluation studies.

Nine formulations of Chlorpropamide were prepared by using various disintegrant in different concentration. The optimized formulation was selected according to the result found from the evaluation parameter of each formulation. Estimation of drug was carried out spectrometrically by UV method. Pre-formulation study involving FTIR showed no interaction between drug and excipients.

The selected drug Chlorpropamide was taken and formulated with different concentration of disintegrant. The tablets were prepared by direct compression technique and then it is punched after subjecting the blend to pre-compression parameters like Angle of repose, Bulk density, Tapped density, Carr's Index, Hausner ratio results obtained were satisfactory. The Post compression parameters like Hardness , Weight variation, Friability, Drug content analysis, Disintegration time (25sec) and *In-vitro* dissolution studies (98.01 at 45 min) were also carried out and tabulated. Among all these formulations F3 was selected as optimized formulation.

All formulations were subjected for four different models viz. Zero order, First order, Higuchi and Peppas model equations and the formulation best fit in to the Higuchi release kinetics that indicate the formulation had released the drug by concentration gradient. It was revealed that super disintegrants and method of formulation had significant influence on drug release.

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