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Formulation and Evaluation of Immediate Release Tablet of Clorazepate

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ABSTRACT

Clorazepate is used to relieve symptoms of anxiety and alcohol withdrawal. It is also used with other medicines to treat partial seizures. Clorazepate is a benzodiazepine. The main objective of the present investigation was to formulate a pharmaceutically active stable immediate release (IR) tablets of Clorazepate using 2 different method like as direct compression method and wet granulation method. The prepared formulations were evaluated using various physical parameters, equipment, dissolution study and drug release profile. The basic approach used in development of clorazepate tablets was that the use of superdisintegrants as like Tablutose, Croscarmellose sodium (CCS), Povidone (PVPK 30) and Hydroxy propyl cellulose (HPC -L) which provide instant disintegration after administration. In-vitro dissolution testing study was carried out for 30 minutes using 0.1N HCl in a dissolution apparatus for evaluation of Drug release. On the basis of the dissolution profile, F5 and F9 gives a better result and were found 100 % release in just 30 minutes and also found that as the polymer ratio were increasing the drug release rate and also increased from the formulation.

INTRODUCTION

1.1 Solid Oral Dosage Form: The oral route is the one most frequently used for drug administration. Oral dosage forms are usually intended for systemic effects resulting from drug absorption through the various epithelia and mucosa of the gastrointestinal tract. Compared with other routes, the oral route is the simplest, most convenient and safest means of drug administration. The most popular oral dosage forms are tablets, capsules. Tablets are prepared by compression and contain drugs and formulation additives, which are included for specific functions, such as disintegrants which promote tablet break-up into granules and powder particles in the gastrointestinal tract, thereby facilitating drug dissolution and absorption. Tablets are often coated, either to provide a protection against environmental factors for drug stability purposes or to mask unpleasant drug taste, as well as to protect drugs from the acid conditions of the stomach (1). Immediate Release Tablet: Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates i.e includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. Immediate release dosage forms are those for which ≥85% of labelled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour (2, 3). In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption.

In this context, the term “release” includes the provision (or presentation) of drug from the formulation to the gastrointestinal tract, to body tissues and/or into systemic circulation. For gastrointestinal tract release, the release is under pH conditions such as pH=1to3, especially at, or about, pH=1. An immediate release pharmaceutical preparation offers: Improved compliance/added convenience, Improved stability, Allows high drug loading, Adaptable and amenable to existing processing and packaging machinery and Cost- effective (4-7). In vitro dissolution testing of solid dosage forms is the most frequently used biopharmaceutical, test method in formulation development. It is used from the start of dosage form development and in all subsequent phases 8. Dissolution testing is a requirement for all solid oral dosage forms and is used in all phases of development for product release and stability testing. It is a key analytical test used for detecting physical changes in an active pharmaceutical ingredient

(API) and in the formulated product. At early stages of development, in-vitro dissolution testing guides the optimization of drug release from formulations. (9-11)

Clorazepate has the characteristics of benzodiazepines. Studies in healthy men have shown that clorazepate has depressant effects on the central nervous system. Since orally administered clorazepate dipotassium is rapidly decarboxylated to form nordiazepam, there is essentially no circulating parent drug. Clorazepate is a benzodiazepine with depressant effects on the central nervous system. Benzodiazepines are able to enhance the binding of gamma-aminobutyric acid (GABA) to the GABA type A (GABA-A) receptor by binding to a region in the extracellular domain found at the interface between the alpha (α) and gamma (γ) subunits of the GABA-A receptor. (12-13) The interaction of GABA and the GABA-A receptor promotes channel opening, leading to an increased chloride influx. Consequently, the use of benzodiazepines, such as clorazepate, leads to neuronal hyperpolarization. Its absorption time is approximately 2 hours with a bioavailability of 91% and the elimination half-life is 50 hours. The usual oral dose is 7.5 mg before bed. In elderly patients, treatment should start with a dose of 3.75 mg before bed. Reduced doses are also recommended in patients with hepatic or renal impairment. (14-15)

2. MATERIALS AND METHODS

2.1 Materials: Clorazepate was received as a gift sample from Unichem Laboratory, Uttar Pradesh, India. Lactose monohydrate, Dibasic calcium phosphate, Sodium starch glycolate, Magnesium stearate, Hypromellose(HPMC E-5), Ethyl cellulose, Diethyl phthalate, Talc, and Iso propyl alcohol were procured from Central Drug House ltd., New Delhi and Loba Chemie Pvt. Ltd., Mumbai.

2.2 Determination of λ_{max}: An accurately weighed 100 mg of Clorazepate is dissolved in pH 6.8 Phosphate buffer and make up the volume upto 100 ml in a volumetric flask (Stock solution: I, mg/ml). From this 10 ml of solution were pipette out and make up the volume upto 100 ml (Stock solution: II), 100 µg/ml). The aliquots were prepared whose concentration ranging from 5-25 µg/ml and the solution was scanned in the UV wavelength of 200-400 nm. The λ max was found to be 255 nm from the concentration of Beer's law ranging from 5-25 µg/ml. (6, 8)

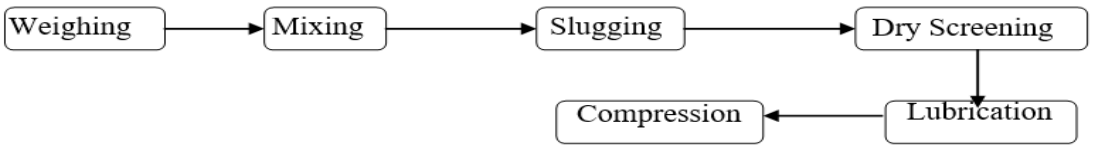
2.3 Identification of Drug by I.R. spectroscopy: The FTIR spectral analysis was carried out by pressed pellet technique. IR spectrum of any substance gives information about the group

present in a specific substance. An IR spectrum of drug was taken using (KBr potassium bromide) pellets. Small quantities of drug sample were mixed with oil, and a drop was placed between KBr pellets and spread uniformly. The pellets were placed in the holder, and an infrared spectrum was taken. The range of scanning was 400-4000 cm^{-1}, different peaks in the infrared spectrum were interpreted for presence of various group in the structure of the drug. (9, 10)

2.4 Compatibility Studies: This work exemplifies a general method of studying the drug excipient interactions, with the aim of predicting rapidly and inexpensively the long-term stability of their mixtures. We study the physico-chemical properties of a drug (clorazepate) in the solid state and in different combinations with several excipients (lactose, mannitol, dibasic calcium phosphate, crosspovidone, povidone). We compare the properties of pure compounds (untreated, or moisture/temperature conditioned) with those of binary mixtures drug: excipient which underwent the same treatment. The purpose is to find indications of interactions within the mixtures, which means a potential incompatibility of the excipient. (10, 11-14)

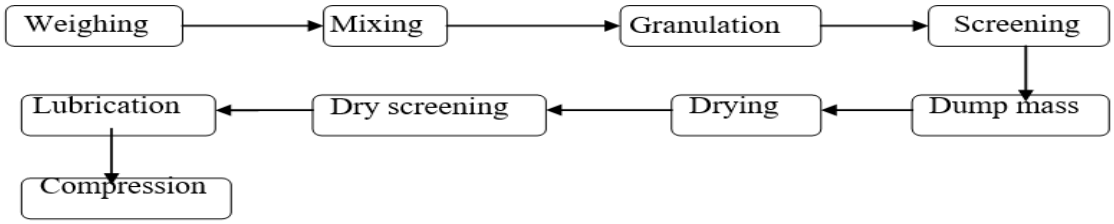
2.5 Formulation Development: Tablets are typically produced using one of the following production processes:

Dry Granulation: The primary powder particles are aggregated under high pressure in dry granulation methods and the powder is squeezed between two rollers to create a sheet of material, or a large tablet is formed in a heavy-duty tableting press; for drugs that do not compress well after wet granulation or are sensitive to moisture, this dry method may be used.



Wet Granulation: The use of a granulating fluid to mass a mixture of dry primary powder particles is known as wet granulation; the fluid contains a solvent that must be volatile and nontoxic in order to be eliminated by drying and water, ethanol, and isopropanol are common liquids, which can be used alone or in combination and the granulation liquid may be used

alone or in combination with a solvent containing a dissolved adhesive to ensure particle adhesion after the granule has dried.



Direct Compression Process: This is the third type of tablet processing, and it is used to produce tablets containing chemicals such as potassium salts. Tablets are made of ammonium chloride and aspirin. Direct compression is possible because these materials have cohesive and flow properties. (15-16)

2.6 Evaluation Of Tablets: The tablets are subjected to the following quality control tests:

I) Weight Variation: The weight variation test is carried out to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average weight was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

II) Hardness: The hardness of tablet is an indication about its strength. Here the force required to break the tablet is measured. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester. (17)

III) Friability Test: Friability is the loss in the weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to find the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula:

$$\% \text{ Friability} = [(W1-W2)100]/W1$$

Where, W1= Weight of tablet before test, W2 = Weight of tablet after test

IV) Disintegration test: The USP device to test disintegration is six glass tubes that are 3cm long, open at the top, and held against 10# screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is positioned in 1 litre beaker of distilled water at 37± 2 ° C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. (18)

V) In Vitro Drug Release Studies: The immediate release tablets are subjected to in vitro drug release studies in 0.1N HCl for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in eight stage dissolution test apparatus using specified volume of dissolution media maintained at 37±10c. The tablets are kept in the cylindrical basket and rotated at 100 rpm ,5ml of the sample from the dissolution medium are withdrawn at each time interval (2, 3, 5, 10, 15 & 30 minutes) and 5ml of fresh medium was replaced each time. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml. (7, 9)

VI) In Vitro Dissolution Kinetic Studies: The drug release data were plotted and tested with zero order (Cumulative % drug released Vs time), First order (Log %Remained Vs time). The zero order release kinetics was shown in Figures. The First order release kinetics were shown in figures. The in vitro dissolution kinetic parameters, dissolution rate constants (K), correlation coefficient ®, the times (t50) for 50% drug released (half life) and dissolution efficiency were calculated and presented in the tables of following chapters. From the slope of linear plots, the dissolution rates were calculated. (19-20)

3. RESULTS AND DISCUSSION

3.1 Development Of Analytical Method By U.V. Spectroscopy (Standard Calibration Curve For Drugs): The λ max of clorazepate was found to be 255 nm by using Double beam UV spectrophotometer. The UV spectrum was shown in the figure 1.

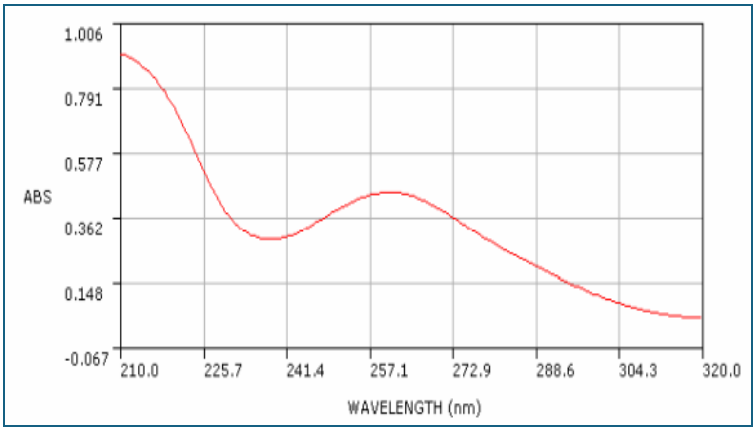


Figure 1: Spectroscopic curve of clorazepate

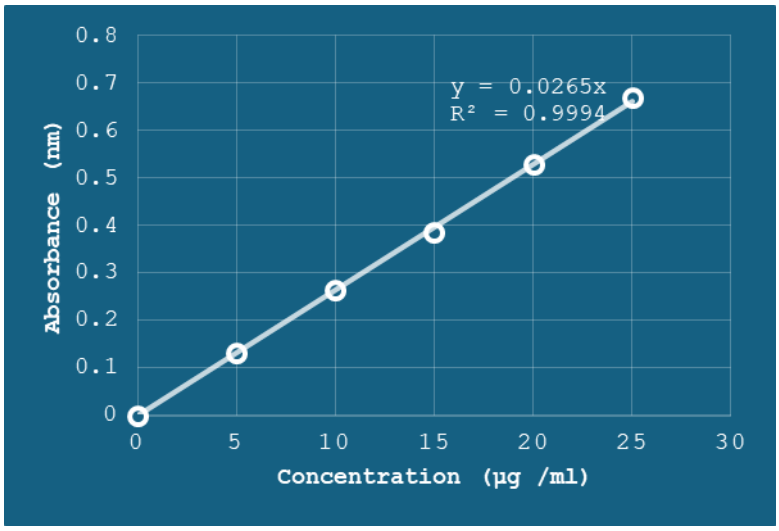


Figure 2: Calibration curve of clorazepate

The calibration curve was plotted for the clorazepate, whose concentration ranging from 5-25 µg/ml and the absorbance were measured at 255 nm using double beam UV spectrometer.

3.2 IR Spectroscopy: The IR spectrum of clorazepate pure drug was found to be similar to the standard spectrum of clorazepate as in IP. The spectrum of clorazepate showed the following functional groups at their frequencies.

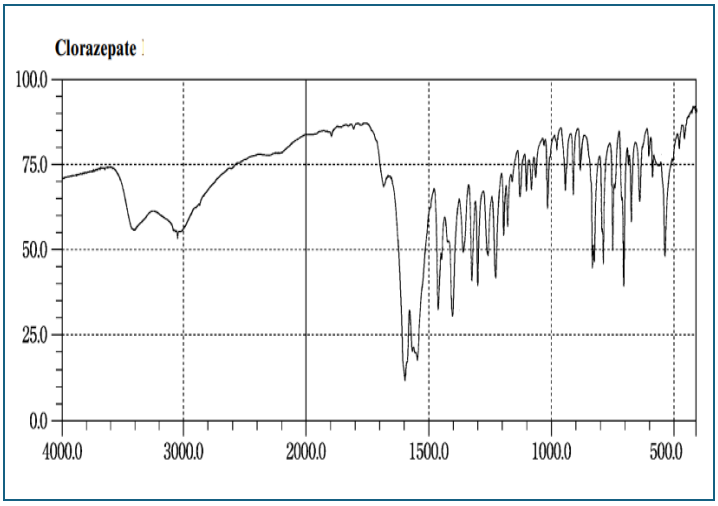


Figure 3: FTIR Spectra of clorazepate (Standard)

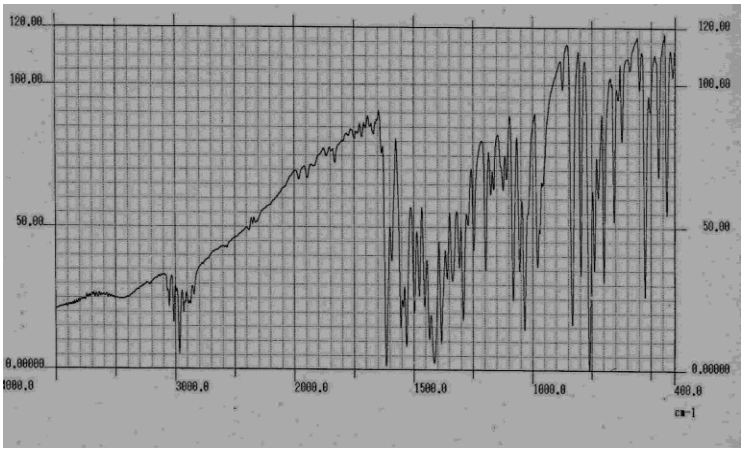


Figure 4: FTIR Spectra of clorazepate (Pure drug)

3.3 Compatibility The physical compatibility evaluation was performed in visual basis. The study implies that the drug, polymer, and other excipients were physically compatible with each other as there was no change of physical description. The samples that were charged in 45 °C/75% RH stability chambers were analysed by IR spectroscopy after 30 days. From the IR studies, it can be concluded that there will be no possible chemical interaction between the excipients and the drugs. So, these excipients were used for the formulation. There is no appearance or disappearance of any characteristic peaks. This shows that there is no interaction between the drug and polymer used.

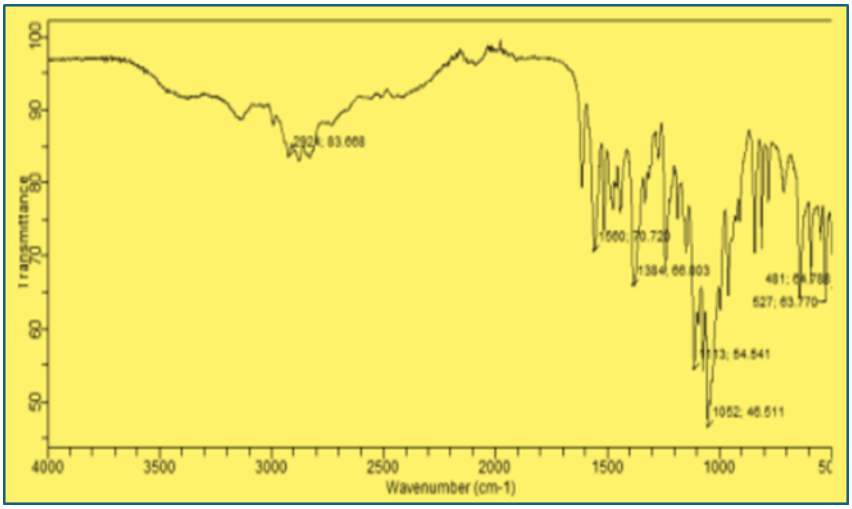


Figure 5: FTIR Spectra of drug with polymer

3.4 Formulation and Development

Table 1: Different formulation and its ingredients

Ingredients	Formulation								
	Direct compression			Wet granulation					
	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Clorazepate	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Tablutose	95.5	-	-	-	-	-	-	-	-
Lactose Monohydrate	-	92.5	-	-	-	-	-	-	-
Microcrystalline cellulose (RQ 102)	-	-	97.5	-	-	16.5	-	-	-
Magnesium stearate	1	1	1	1	1.6	1.20	0.5	1	1
Colloidal silicon dioxide	1	1	1	1	1.6	-	-	-	1
Lactose	-	-	-	45	60	67.80	-	75	75
Microcrystalline cellulose –IP	-	-	-	35	48	-	-	-	-
Povidone (PVPK 30)	-	-	-	1.5	2	-	-	-	3
Starch	-	-	-	-	20	7.5	7.5	9	9
Talc	-	-	-	-	-	2.2	2.2	3.5	3.5
Croscarmellose sodium (CCS)	-	-	-	-	-	-	-	7	7
Microcrystalline cellulose (PH -101)	-	-	-	-	-	28.8	108.8	19	19
Hydroxy propyl cellulose (HPC -L)	-	-	-	-	-	1.5	-	-	-

3.5 POST COMPRESSION EVALUATION

I) Weight variation: Results are given in table below. From the above observations it was concluded that F7 batch had maximum deviation range where as F1 had lowest range.

Table 2: Weight variation and drug content study of F1 to F9

Sl. no.	Formulation	Weight variation	Drug content
1	F1	102.5 ± 1.12	88.44
2	F2	99.5 ± 5.12	86.23
3	F3	104.5 ± 5.75	93.22
4	F4	88.5 ± 3.83	94.86
5	F5	138.7 ± 4.76	98.51
6	F6	130.5 ± 2.75	83.29
7	F7	133.4 ± 5.98	79.81
8	F8	119 ± 3.12	92.37
9	F9	123.5 ± 2.63	99.72

II) Dimension and Hardness: The tablet dimension like tablet "thickness and diameter was determined using a vernier caliper by taking 10 tablets from each and calculating average" value. From observation it was concluded that tablets of all batches had good hardness and uniform thickness.

Table 3: Hardness and dimension studies of batches F1 to F9

Batch No.	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)
F1	1.0 – 1.5	3.31 – 3.39	5.10 – 5.12
F2	1.5 – 2.0	3.25 – 3.32	5.10 – 5.14
F3	2.5 – 3.5	3.33 – 3.38	5.10 – 5.16
F4	2.0 – 2.5	3.42 – 3.48	5.11 - 5.15
F5	3.0 -3.5	3.43 – 3.52	6.10 – 6.22
F6	3.5 – 4.5	3.45 – 3.51	7.26 – 7.30
F7	2.5 – 3.0	2.45 – 2.53	7.12 – 7.18
F8	2.5 – 3.0	3.25 – 3.29	6.08 – 6.14
F9	3.0 – 3.5	3.35 – 3.29	5.19 – 5.22

III) Friability: Friability of the tablets was determined using Roche friabilator. The friability of clorazepate tablets in table all formulation were found within the limits except formulation no F1and F3 specified in JP (friability <1%).

Table 4: Friability study of batches F1 to F9

Batch No.	Initial Weight (W_1) gm	After Weight (W_2) gm	Friability (%)
F1	1.976	1.953	1.98
F2	1.883	1.823	0.33
F3	2.184	1.995	3.34
F4	1.578	1.255	1.17
F5	2.251	2.355	1.21
F6	1.264	1.574	1.31
F7	2.245	2.360	1.5
F8	1.655	2.342	.0.39
F9	2.276	2.460	0.32

IV) In vitro disintegration: The time required for the tablet to disintegrate was calculated by placing Tablet in water in disintegration apparatus at 37 °C.

Table 5: Disintegration time of F1 to F9

Sl. No.	Formulation	Disintegration time	
		Mint.	Sec.
1	F1	-	19
2	F2	1	50
3	F3	-	-
4	F4	-	16
5	F5	1	6
6	F6	2	13
7	F7	-	17
8	F8	1.5	26
9	F9	0.5	11

V) In-vitro dissolution: In vitro dissolution of clorazepate immediate release tablets were studied in USP type-II dissolution apparatus employing a paddle stirrer at 50 rpm using 900 ml water as dissolution medium at 37º C. Six tablets were used in each test.

Table 6: In-vitro % release of batches F1 to F9

Formulation	% release
F1	78.97-82.77
F2	75.66-80.24
F3	78.65-83.65
F4	80.52 - 85.20
F5	95.02 - 100.42
F6	83.49 - 85.92
F7	50.54 - 59.71
F8	87.98 - 91.56
F9	97.83 - 100.69

Table 7: In-vitro release profile of batches F5 & F9

Time (mint.)	% Cumulative drug release	
	F5	F9
0	0	0
5	25.344	32.544
10	55.817	66.524
15	70.681	77.095
20	83.316	86.911
25	92.235	95.217
30	95.208	98.237

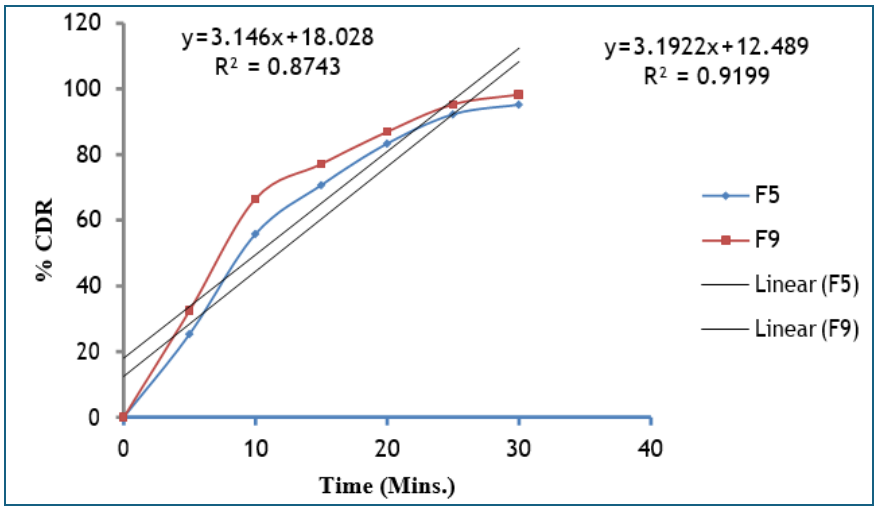


Figure 6: Zero order drug release for the batches F5 and F9

Table 8: In-vitro release profile of batches F5

Time (min.)	Abs.	Amount in 900 ml (mg)	% drug release	Cumulative drug release	% drug retain	Log % drug Retain
0	0	0	0	0	100	2.000
5	0.278	25.012	25.344	25.344	74.656	1.873
10	0.612	55.086	30.473	55.817	44.183	1.645
15	0.775	69.756	14.865	70.681	29.319	1.467
20	0.914	82.225	12.635	83.316	16.684	1.222
25	1.011	91.027	8.919	92.235	7.765	0.890
30	1.044	93.961	2.973	95.208	4.792	0.681

Table 9: In-vitro release profile of batches F9

Time (min.)	Abs.	Amount in 900 ml (mg)	% drug release	Cumulative drug release	% drug retain	Log % drug Retain
0	0	0	0	0	100	2.000
5	0.278	25.012	25.344	25.344	74.656	1.873
10	0.612	55.086	30.473	55.817	44.183	1.645
15	0.775	69.756	14.865	70.681	29.319	1.467
20	0.914	82.225	12.635	83.316	16.684	1.222
25	1.011	91.027	8.919	92.235	7.765	0.890
30	1.044	93.961	2.973	95.208	4.792	0.681

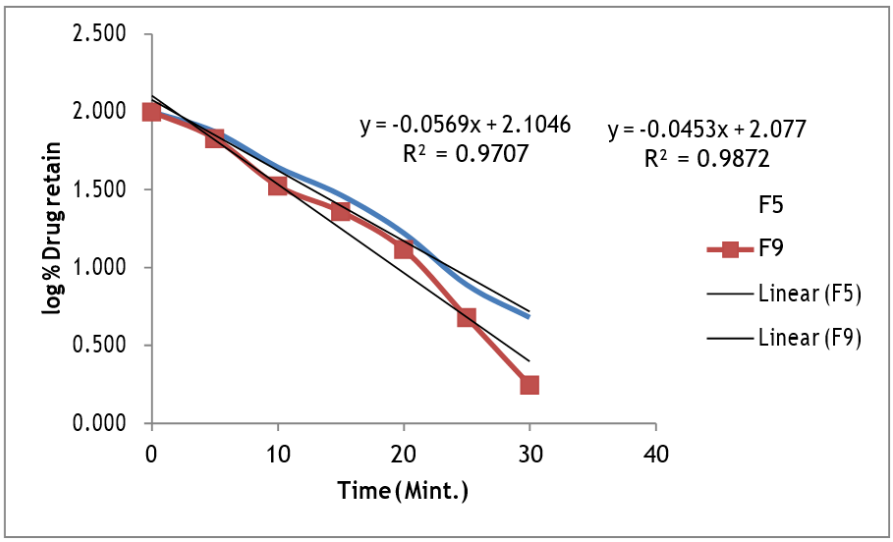


Figure 7: First order drug release for the batches F5 and F9

Table 10: R^2 value for F5 and F9 formulation

Formulation	Zero order release	First order release
F5	0.9199	0.9872
F9	0.8743	0.9707

4. CONCLUSION

Clorazepate immediate release tablet different batches were prepared using different disintegrants. First start with dry mixing preparation for F1 to F3 formulation but suitable preparation does not form. After dry mixing from F4 to F9 batches were prepared by wet granulation method. Water, IPA, DCM and PVP used for binding solution we tried single or combination for reaching maximum release and ended with combination form of IPA, DCM and PVP. The prepared tablet batches were subjected to various physical, physiochemical and

in-vitro dissolution investigation and analysis for best batch. Total nine batches immediate release tablets were prepared among them F5 and F9 were found satisfactory. Between F5 and F9 better in-vitro dissolution release was seen in F9 batch. F8 and F9 approximately similar formula only different in colloidal silicon dioxide is extra added in F9 which gives better dissolution value for F9. In-vitro characterization of clorazepate immediate release tablets was done all data were comply with specification for the marketed product so the batch is kept further for stability study to expose to the market.

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