ejpmr, 2022, 9(4), 319-326

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION, EVALUATION AND OPTIMIZATION OF FAST DISINTEGRATING CLOPIDOGREL TABLETS

***[1]Aswathi V., [2]Sujith S. Nair and [3]Sreena K.**

*[1,2,3]Crescent College of Pharmaceutical Sciences, Payangadi, Kannur, Kerala.

***Corresponding Author: Aswathi V.**

Crescent College of Pharmaceutical Sciences, Payangadi, Kannur, Kerala.

Article Received on 02/02/2022 **Article Revised on 22/02/2022** **Article Accepted on 13/03/2022**

ABSTRACT

The main objective of the research work is to formulate the Clopidogrel fast disintegrating tablets. Clopidogrel, an antiplatelet drug used to control heart attack, hypertension by inhibiting platelet activation and aggregation. Fast disintegrating tablets disintegrate or dissolve quickly in the saliva without the need of water. The fast dissolving tablets of Clopidogrel were prepared employing different concentrations of sodium starch glycolate, crospovidone and croscarmellose sodium in different combinations as a Superdisintegrant by direct compression technique. FTIR studies for drug & excipients revealed that there is no incompatibility/ interaction between drug and excipients. The developed formulation were then charecterised for their physical appearance, bulk density, tapped density, carr's index, hausner's ratio, angle of repose, weight variation, hardness, friability, drug content, thickness, *in vitro* disintegration, *in vitro* dissolution and stability studies. The fast disintegrating tablets prepared using sodium starch glycolate, crospovidone and croscarmellose sodium as superdisintegrant showed better result and hence selected as optimized formulation. The optimized formulation was subjected to stability studies under 3 different conditions. From the stability studies after 90 days, it was found that there was no significant change in appearance drug content, friability, hardness, *in vitro* disintegration and *in vitro* dissolution. The *in vitro* drug release from the tablets showed significantly improved drug dissolution with an increase in concentration of the superdisintegrants. Hence these fast dissolving tablet dosage form could be a potential formulation which could improve the bioavailability reducing the dosing frequency, improved patient compliance.

KEYWORDS: Clopidogrel, fast disintegration tablets, direct compression, superdisintegrants.

1. INTRODUCTION

Drug delivery systems are strategic tool for expanding markets/ indications, extending product life cycles and generating opportunities. Dosage form is a transformation of pure chemical compound into a predetermined form by admixing drug component with different kind of non drug component (excipients). Various types of dosage form are available such as tablets, capsules, syrup, suppositories, patches, injections having different type of drug delivery mechanism. These classical dosage forms have some advantages and disadvantages. In order to get the desired therapeutic effect and minimum adverse effect drug should be delivered to its site of action. Depending upon the route of administration dosage forms are different type include liquid, solid semisolid dosage forms, this include syrup, tablets, capsules, pills. Oral route of drug administration have wide acceptance up to 55-60%of total dosage form. Solid dosage forms are popular because an ease of administration, accurate dosage, self medication, patient compliance, pain avoidance.[1] The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the paediatric and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form.[2] The problem of swallowing is a common phenomenon in a geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to under developed muscular and nervous system and in schizophrenic patients which leads to poor patient compliance. The basic approaches used in development of mouth dissolving tablet is the use of superdisintegrants, which provide instantaneous disintegration of tablet after putting on the tongue, there by releasing the drug in saliva. In such cases bioavailability of drug is greater due to absorption of drug in oral cavity, and also due to pregastric absorption of saliva containing dispersed drug that pass down into stomach, as well as amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets. In a fast dissolving drug delivery system, the tablet will dissolve and disintegrate in saliva without the need of water.[3]

2. METHODOLOGY

2.1 MATERIALS

Clopidogrel, microcrystalline cellulose, crospovidone and croscarmellose sodium was purchased from yellow chem. Products Mumbai. Sodium starch glycolate and mannitol obtained from E merck Mumbai, magnesium stearate and talc procured from ozone international Mumbai.

2.2 PREFORMULATION STUDIES

Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

2.2.1 Identification by FTIR spectroscopy

The spectra were taken by using Shimadzu FTIR 8400 spectrophotometer and were compared with standard spectra. In this study pelletisation of potassium bromide (KBr) was employed. Before forming the pellet of potassium bromide, it was completely dried at 100 °C for one hour and after drying it was thoroughly mixed with the sample in the ratio of 1 part of sample and 100 parts of KBr. The mixture was compressed to form a disc using dies. This disc was placed in the sample chamber and a spectrum was obtained through the software program which was further subjected to interpretation.[4,5]

2.2.2 DRUG – EXCIPIENT COMPATIBILITY STUDIES:

While designing the formulation of fast dissolving tablets, it is important to give considerations on drug exipient interaction within the system. So it is necessary to find out that if there is any interaction between Clopidogrel and exipients used in the formulation. The study was conducted using Fourier Transform Infrared Spectroscopy (FTIR).[7,8]

2.2.3 PRECOMPRESSION ANALYSIS OF PREPARED POWDER BLEND

The flow properties of powder blend were evaluated in terms of their bulk density, tapped density, angle of repose, Carr's index and hausner's ratio.[9-16]

2.3 FORMULATION OF FAST DISSOLVING TABLETS OF CLOPIDOGREL EXPERIMENTAL DESIGN

Design Expert Stat Ease Software was used to design formulations. Seventeen formulations with different superdisintegrant, sodium starch glycolate, crospovidone, croscarmellose sodium were suggested by the software (Design Expert Stat).

Table no. 1: Preparation of fast disintegrating tablets.

Name of ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)	F13 (mg)
Clopidogrel	75	75	75	75	75	75	75	75	75	75	75	75	75
MCC	70	70	70	70	70	70	70	70	70	70	70	70	70
Sodium starch Glycolate	29	14.5	0	0	14.5	14.5	0	14.5	29	0	29	29	14.5
Crospovidone	14.5	14.5	14.5	0	29	0	29	29	0	14.5	14.5	29	0
Croscarmellose sodium	0	14.5	0	14.5	29	0	14.5	0	14.5	29	29	14.5	14.5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2
Mannitol	54.5	54.5	83.5	83.5	25.5	83.5	54.5	54.5	54.5	54.5	25.5	25.5	69

2.3.1 PREPARATION

The calculated amounts of Clopidogrel, superdisintegrant and microcrystalline cellulose were accurately weighed and mixed for five minutes. Thereafter, the formulation weight of mannitol was mixed with the microcrystalline - superdisintegrant mixture for 10 minutes. Then correct amount of magnesium stearate was added with the powder blend for a further 2 minutes. After mixing, the powder blend was compressed into tablets weighing 250 mg.[17]

2.4 EVALUATION OF FASTDISSOLVING TABLET OF CLOPIDOGREL

2.4.1 General Appearance

The general appearance of a tablet, its visual identity and overall elegance, is essential for consumer acceptance. The prepared tablet was evaluated for its colour, odour and taste.[6]

2.4.2 Thickness

Thickness of tablets was measured by using micrometer. The number of divisions on pitch scale (PSR-pitch scale reading) that coincide with head scale reading was noted and least count was determined. The tablet was placed in between two parallel surfaces of screw gauge. The position of tablet was changed and 3 readings were taken and recorded and calculated the average of three readings.[18]

2.4.3 Weight variation

Weight of the tablet being made is routinely measured to ensure that a tablet contains the proper amount of drug. 10 Tablets were randomly selected and individually

weighed and calculated the average weight and compared the individual tablet's weight to the average weight.[18]

2.4.4 Hardness

The hardness can be tested using Monsanto hardness tester. The tablet to be tested was held between a fixed and a moving jaw of Monsanto Hardness Tester. The force applied to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet breaks. The reading was noted from the scale which indicates the pressure required to break the tablet. The hardness of a tablet depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression.[17,18]

2.4.5 Friability

Friability test can be performed to evaluate the ability of the tablets to withstand abrasion in acking, handling and transporting. The test is performed using friability test apparatus. The Friabilator consists of a plastic chamber divided in to two parts and revolves at 25 rpm. Six tablets were weighed and placed in the tumbling chamber and rotated for four minutes at 100 revolutions. During each revolution the tablets fall from a distance of six inches to undergo shock. After 100 revolutions the tablets were again weighed. The loss in weight indicates the friability.[21,27,28]

2.4.6 Drug content

An orally disintegrating Clopidogrel tablet weighing 250mg and equivalent to 75 mg Clopidogrel was accurately weighed, finely powdered, and transferred into a volumetric flask. About 60 mL of 0.1 N HCl was added and the flask was sonicated for 10 min, then shaken mechanically for 30 min and the volume made up to 100 mL with the same solvent, followed by sonication and filtration. The drug content was determined spectrophotometrically at 240 nm.[21]

2.4.7 Disintegration

6 Tablets were placed into the tube of disintegration apparatus and placed in 1litre beaker containing phosphate buffer (pH 6. 8) at 37± 2˚ C. Floating of tablets can prevented by placing perforated plastic disc on each tablet. The time of disintegration was recorded.[19,20]

2.4.8 Dissolution

900 ml of phosphate buffer (pH 6. 8) was taken in the dissolution vessel. Temperature was maintained at 37± 5˚ C. Tablets were placed in the vessels containing buffer. The paddles were rotated at 50 rpm. 1ml of sample from each vessel was withdrawn at an interval of 2, 4, 6, 8, 10, 12, 14, 16 minutes and was made up to 10 ml using phosphate buffer (pH 6.8). Replace with equal volume of fresh phosphate buffer on each withdrawl. The absorbance was measured at 240 nm using UV spectrophotometer.[22,23,24]

2.5 OPTIMIZATION

Optimization of the formulation was studied by Box Benhken design. In the study, SSG, CP, and CCS were selected as the three factors and *in vitro* disintegration time and *in vitro* drug release were considered as the two responses. Hence, seventeen experimental trials were done. Trials were repeated twice to evaluate experimental errors and increase power ratio. Contour plots were drawn and optimum formulation was selected by optimization criteria.[25,26]

2.6 STABILITY STUDIES

The stability studies were carried out of the most satisfactory formulation as per ICH guidelines Fast dissolving tablets were packed in wide mouth air tight glass container. Stability studies were carried out according to ICH and WHO guidelines by storing the formulations at 40ºC ± 2°C at 75 ± 5%, 25ºC ± 2ºC at 60% ± 5% RH, 5ºC ± 2ºC RH for period of three months, and parameters evaluated hardness, friability, content uniformity, *in vitro* disintegration time, wetting time and *in vitro* drug release.[24]

3. RESULTS

3.1 Organoleptic properties of Clopidogrel

Table no 2: Organoleptic properties of Clopidogrel.

Colour	Off-white
Odour	Odourless
Taste	Bitter

3.2 Identification and Compatibility by FTIR studies

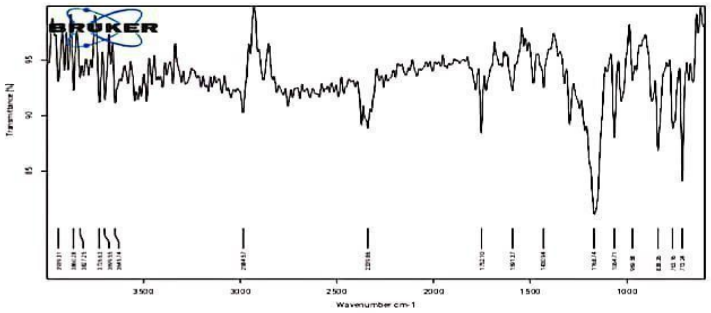

Fig no. 2 FTIR Spectrum of Pure drug (Clopidogrel).

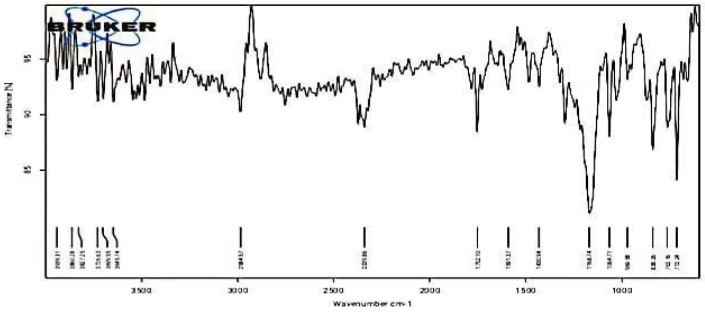

Fig no. 3 FTIR Spectrum of Drug + Sodium starch glycolate.

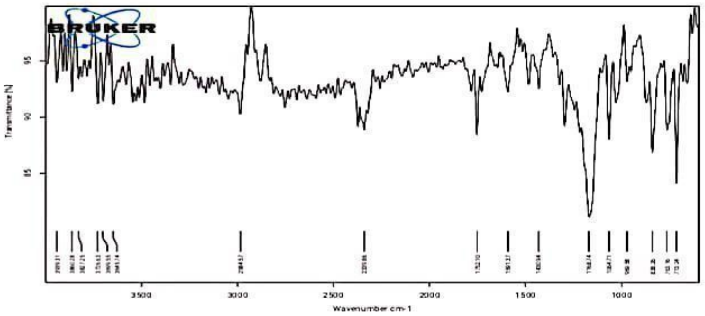

Fig no. 4 FTIR Spectrum of Drug + Crospovidone.

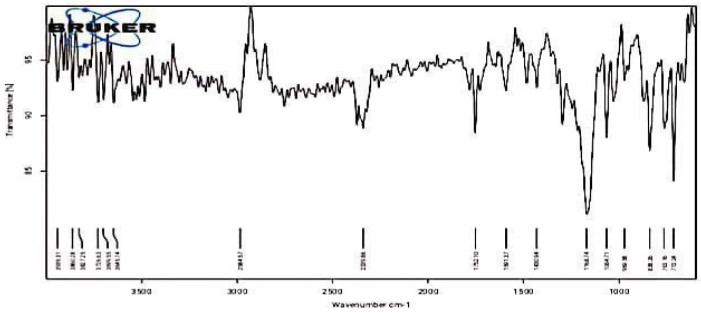

Fig no. 5 FTIR Spectrum of Drug + Croscarmellose sodium.

3.3 PRE COMPRESSION STUDIES FOR POWDER BLEND

Table no 4: Pre compression evaluations.

Formulation code	Bulk density(g/ml) ±SD	Tapped density(g/ml) ±SD	Angle of repose(θ) ±SD	Carr's index(%) ±SD	Hausners ratio ±SD
F1	0.41±0.01	0.45±0.02	33.7±0.134	11.19±0.01	1.12±0.015
F2	0.38±0.01	0.42±0.01	28.1±0.24	9.58±0.04	1±0.14
F3	0.39±0.002	0.45±0.002	30.3±0.147	12.4±0.002	1.15±0.01

F4	0.42±0.001	0.46±0.005	31.4±0.245	10.1±0.004	1.13±0.002
F5	0.41±0.004	0.47±0.003	31±0.146	11.39±0.02	1.14±0.004
F6	0.44±0.007	0.45±0.006	31±0.146	10.2±0.001	1.11±0.01
F7	0.41±0.003	0.43±0.003	30.6±0.165	9.87±0.003	1.10±0.001
F8	0.38±0.002	0.44±0.002	31.1±0.114	10.1±0.004	1.13±0.02
F9	0.39±0.01	0.41±0.001	31.4±0.119	12.4±0.002	1.14±0.011
F10	0.43±0.007	0.45±0.001	29.3±0.169	10.1±0.04	1.13±0.002
F11	0.41±0.004	0.43±0.009	28±0.214	10.2±0.001	1.10±0.001
F12	0.43±0.007	0.43±0.003	29.4±0.242	9.8±0.004	1.12±0.04
F13	0.33±0.002	0.44±0.006	30.2±0.2	11.38±0.04	1.12±0.15

All values are expressed as mean ± SD, n = 3

3.4 POST COMPRESSION STUDIES

Table no. 5: Post compression evaluation of fast disintegration Clopidogrel tablet.

Weight variation (mg)	Friability(%)	Hardness (kg/cm^2)	Drug content(%)	Thickness(mm)	*In vitro* disintegration (min)	*In vitro* drug release(%)
250±0.39	0.54±0.013	4.42±0.15	99.78±0.0111	4.01±0.12	0.60±0.02	99±0.301
249±0.68	0.56±0.011	4.21±0.14	99.84±0.313	4.03±0.16	0.65±0.054	99.4±0.602
250±0.540.63	0.511±0.017	4.8±0.12	99.3±0.125	4.02±0.13	0.68±0.01	98±0.313
247±0.61	0.513±0.028	4.7±0.11	99.61±0.125	4.1±0.12	0.679±0.65	98±0.461
249±0.73	0.62±0.015	4±0.013	99.8±0.2145	4.08±0.1	0.61±0.001	99.5±0.346
249±0.38	0.512±0.023	4.75±0.11	99.85±0.5123	4.02±0.13	0.621±0.068	97.97±0.21
251±0.72	0.523±0.043	4.61±0.16	99.03±0.2113	4.06±0.11	0.6421±0.064	99±0.27
249±0.051	0.524±0.0417	4.61±0.14	99.30±0.315	4.1±0.03	0.6315±0.15	98.94±0.42
249±0.007	0.53±0.013	4.53±0.128	99.08±0.415	4.03±0.17	0.65±0.064	98.89±0.21
247±0.003	0.52±0.011	4.78±0.1	99.30±0.205	4.02±0.13	0.634±0.049	98.9±0.131
249±0.087	0.541±0.2	4.42±0.03	99.8±0.145	4.01±0.11	0.599±0.034	99.68±0.19
248±0.73	0.54±0.017	4.4±0.04	99.61±0.154	4.1±0.12	0.61±0.91	99.32±0.31
248±	0.57±0.03	4.11±0.013	99.3±0.121	4.02±0.13	0.62±0.091	98.9±0.456

All values are expressed as mean ± SD, n = 3

3.5 OPTIMIZATION

The formulation is optimized by Design expert Software version 13.0.7.0. Box-Behnken design was used to find the optimized formulation. 13 formulations were suggested by the software and after optimization of the analyzed data, 24 solutions were obtained. From the 24 solutions, one was selected by considering the *in vitro* disintegration and *in vitro* drug release. The batch with 29mg of sodium starch glycolate, 14.5 mg of crospovidone, 29 mg of croscarmellose sodium was found to be optimum. From this data, formulation F11 was selected as the optimized formulation.

The formulation F11 showed highest value for *in vitro* drug release. Hence, the data obtained from the *in vitro* drug release was used for stability studies, conducted on selected formulation as per ICH guidelines.

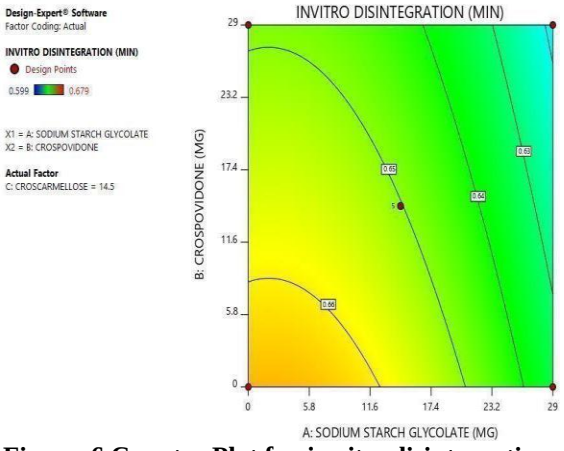

Fig no: 6 Counter Plot for *in vitro* disintegration.

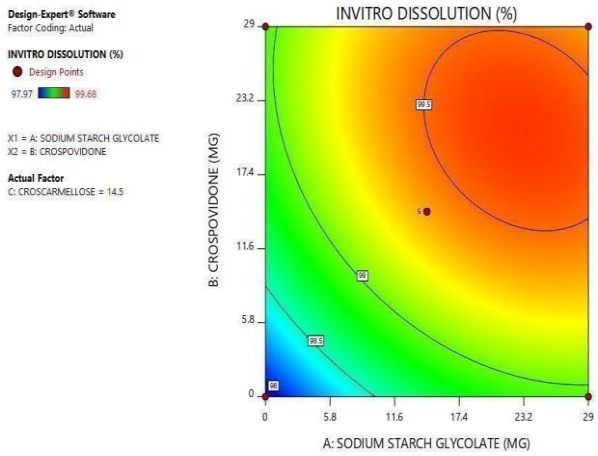

Fig no: 7 Counter plot for *in vitro* dissolution.

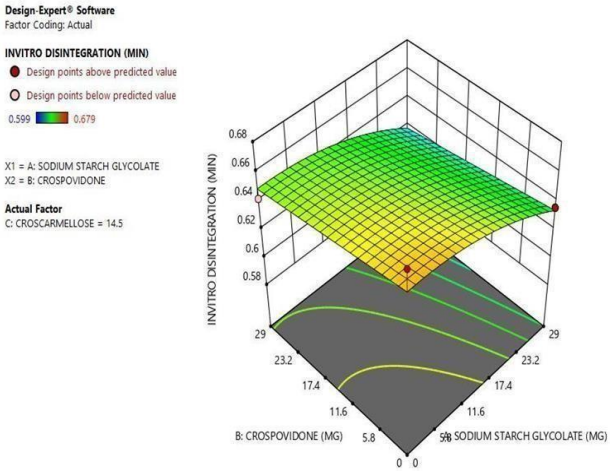

Fig no: 8 3-D Surface plot for *in vitro* disintegration.

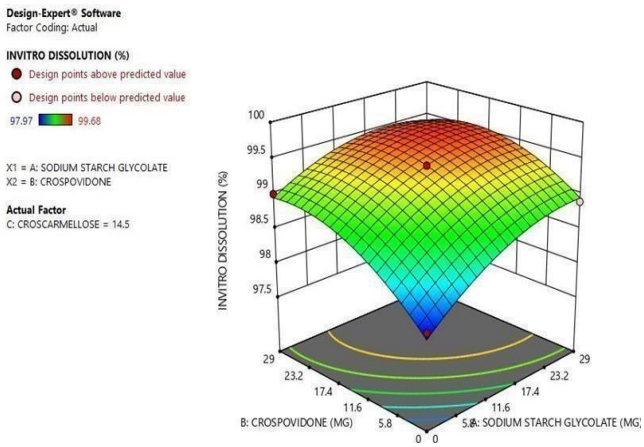

Fig no: 9 3-D Surface plot for *in vitro* dissolution.

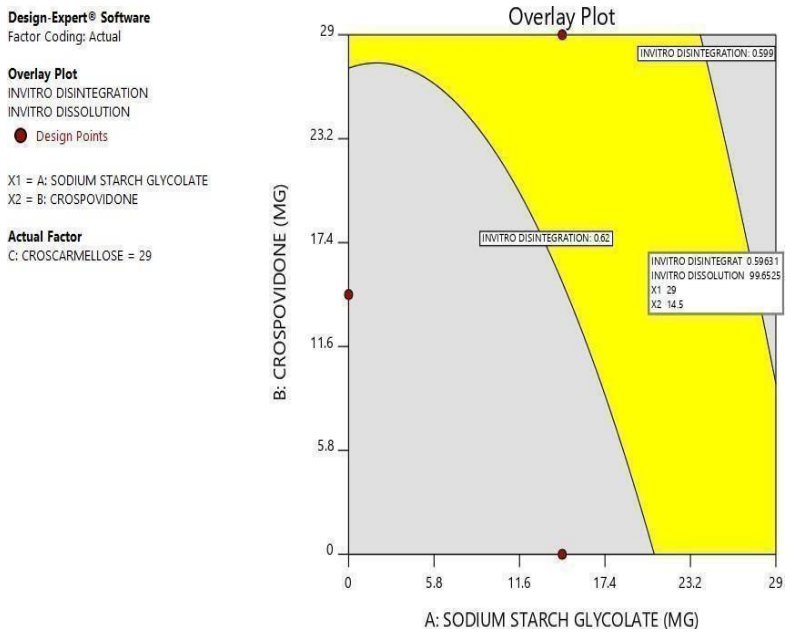

Figure no: 10 overlay plot.

3.6 STABILITY STUDY DATA

The optimized formulation F11, containing SSG, CP, CCS as superdisintegrants was evaluated at 3different storage conditions.

Table no 6: Stability studies of fast disintegration tablets.

Formulation code	Storage condition	Sampling interval	Appearance	Drug content(%)	Hardness (kg/cm^2)	Friability (%)	*In vitro* disintegration (min)	*In vitro* dissolution (%)
	40°C±	30	Off-white	99.8±0.41	4.42±0.1	0.54±0.12	0.599±0.034	99.68±0.01
	2°C at 75% RH±	60	Off-white	99 ±0.1	4.4±0.54	0.51±0.11	0.54±0.031	99±0.013
	5% RH	90	Off-white	98.499±0.2	3.4±0.24	0.41±0.51	0.49±0.001	97.13±0.11
F11	25°C± 2°C	30	Off-white	99.4±0.45	4.13±0.11	0.5±0.23	0.5±0.005	99.6±0.072
	at 60%RH ± 5% RH	60	Off-white	99±0.45	4.11±0.2	0.49±0.31	0.43±0.045	99.2±0.061
		90	Off-white	98±0.04	3.13±0.7	0.42±0.25	0.41±0.16	99±0.001
	5°C ± 2°C	30	Off-white	99±0.45	4.42±0.01	0.52±0.42	0.59±0.24	99.61±0.031
		60	Off-white	97±0.035	4±0.1	0.5±0.26	0.54±0.31	98.54±0.031
		90	Off-white	96.59±0.21	3.31±0.3	0.45±0.11	0.49±0.49	98±0.061

All values are expressed as mean ± SD, n = 3

4 CONCLUSION

Clopidogrel fast disintegration tablets were successfully developed using sodium starch glycolate, crospovidone, croscarmellose sodium as superdisintegrants with simple and feasible manufacturing process. FTIR studies for drug & excipients revealed that there is no incompatibility/ interaction between drug and excipients. The developed formulation were then charecterised for their physical appearance, bulk density, tapped density, carr's index, hausner's ratio, angle of repose, weight variation, hardness, friability, drug content, thickness, *in vitro* disintegration, *in vitro* dissolution and stability studies.

The fast disintegrating tablets prepared using 29 mg sodium starch glycolate, 14.5 mg crospovidone and 29 mg croscarmellose sodium as superdisintegrant show better result and hence selected as optimized formulation. F11 was subjected to stability studies under 3 different conditions. From the stability studies after 90 days, it was found that there was no significant change in appearance drug content, friability, hardness, *in vitro* disintegration and in *vitro* dissolution. The *in vitro* drug release from the tablets showed significantly improved drug dissolution. Hence these fast dissolving tablet dosage form could be a potential formulation which could improve the bioavailability reducing the dosing frequency, improved patient compliance.

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