WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 8, 1421-1437. Research Article ISSN 2277– 7105

"FORMULATION, DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF PRASUGREL HYDROCHLORIDE"

R. Margret Chandira*[1], P. Palanisamy[1], B.Jaykar[1], A.Pasupathi[1], N. K. K. Sreedharan[1], Debjit Bhowmic[2]

[1]Department of Pharmaceutics, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's University, Salem (D.T), Tamil Nadu, India.

[2]Department of Pharmaceutics, Nirma College of Pharmacy, Vijayawada, (A.P), India.

Article Received on
22 May 2015,

Revised on 15 June 2015,
Accepted on 08 July 2015

***Correspondence for Author**
R. Margret Chandira
Department of Pharmaceutics, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's University, Salem (D.T), Tamil Nadu, India.

ABSTRACT

The aim of present investigation wss to develop immediate release formulation of Prasugrel Hydrochloride for oral drug delivery by using suitable concentration of superdisingrants. Croscarmellose sodium (AC-DI-SOL), povidone, MCC, Magnesium stearate was used to formulate the immediate release tablet. Croscarmellose sodium was used as superdisintegrant and povidone was used as a binder to control the release of drug. Special care was taken for Prasugrel Hydrochloride processing in low humidity condition and geometric mixing is applied to avoid content uniformity and segregation. The flow properties of the powdered blend for all the batches were found to be good and free flowing. The weight variation, hardness and friability of all the formulated tablets within the specified requirements. The disintegration times for the formulated tablets are within the range of USP. For Prasugrel Hydrochloride tablets direct granulation was method of choice. Results found that release profile of batch no.F6 matches with Innovator product. The Percentage cumulative drug release of batch. No. F6 was found at 30 Minutes 103.12%.

KEYWORDS: Prasugrel Hydrochloride, Immediate release, Croscarmellose sodium, povidone.

INTRODUCTION

The convenient oral drug delivery has been known for decades is the most widely utilized route of administration among all the routes. It remains the preferred route of administration in the discovery and development of new drug candidates. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improve the shelf life of the product**(1).** Immediate release tablets are designed to disintegrate and release the drug in absence of any controlling features such as coating or other formulation techniques. Despite a rising interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole, disintegrating and releasing their medicaments rapidly in the gastrointestinal tract. A Disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Such a rapid rupture of the tablet matrix increases the surface area of the tablet particles, Thereby increasing the rate of absorption of the active ingredient and producing the desired therapeutic action [(2)]. The proper choice of Disintegrant and its consistency of performance are critical to formulation development of immediate release tablets. In the past, starch was one of the most widely used, Inexpensive, and effective tablet disintegrants. A high concentration of starch is required to bring about effective disintegration.[1-3]

Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. Tablet is the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing; however in many cases immediate onset of action is required than conventional therapy. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms, mainly because they are easy to administer and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities.

Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques.

Tablets for immediate release often consist of filler, a binder, lubricants and disintegrants. In many cases, the disintegration time of solid dosage forms is too long to provide appropriate

therapeutic effect. To improve the disintegration time, so-called superdisintegrants are used. Superdisintegrants are used to improve the efficacy of solid dosage forms. This is achieved by decreasing the disintegration time which in turn enhances drug dissolution rate. P2Y12 inhibitors such as prasugrel do not change the risk of death when given to people who have had a NSTEMI. They do however increase the risk of bleeding and decrease the risk of further cardiovascular problems. Thus their routine use is of questionable value.[4-5]

MATERIALS AND METHODS

Materials

Prasugrel Hydrochloride was received as a gift sample from Caplin Point Research Laboratory. Calcium carbonate, Lactose DCL-11 and MCC pH-102 was gifted by FMC Bio-polymer (India). Croscarmellose sodium and Cross povidone was gifted by Chetan & Chetan (India). Purified Talc, Sodium starch glycolate and calcium stearate was gifted by Cabot Sanmer (India).

STANDARD CALIBRATION CURVE OF PRASUGREL HYDROCHLORIDE

Prasugrel hydrochloride 25 mg was accurately weighed and transferred into a 50 mL of volumetric flask and dissolved in methanol make upto 50 with methanol. The solution was observed to contain 500µg/mL. A series of dilutions were made from the above stock solution to get the solution of concentration ranging from 1 to 10 µg/ml. Absorbance of solutions was measured spectrophotometrically at 249 nm. The results are shown in Table. No: 1 & Figure. No: 1.

SPECTRAL IDENTIFICATION[6-7]

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, to promote the consistent release and bioavailability of the drug and protect it from degradation.

Infra red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

Method

Compatibility study was performed by preparing compatibility blends at different ratios of different excipients with the drug, based on tentative average weight. These blends were

stored at accelerated condition of 40°C/75% RH. Control samples were stored at 40°C. The ratio of drug to excipient varies from 1:1 to 1:10 depending on the purpose of use, and the samples were kept in double lined poly-bags. The samples were evaluated for any change in the physical characteristics with reference to its controlled sample stored at 40°C for a period of 30 days.

In the present study, the potassium bromide disc (pellet) method was employed. Chemical stability was confirmed by IR spectrometry. The results are shown in Figure. No: 2-6.

Preformulation Studies of pure drug and excipients[8-10]

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical recipients in the dosage form. Hence, the following preformulation studies were performed on the obtained sample of drug.

Pre compression parameters[11]

The properties of the tablets like content uniformity, stability, disintegration time, dissolution profile, hardness and friability depends on the granule parameters. The properties of granules, which are of most importance, are residual bulk density, Tapped density, compressibility index and the angle of response. The same were evaluated in laboratory condition. Granule parameters were carried out after lubrication.

Solubility

It determined by dissolving drug substance in freely soluble in water, slightly soluble in ethanol (95%), practically insoluble in chloroform and in ether.

Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by:

$D_b = M / V_b$

Where, M is the mass of powder

V_b is the bulk volume of the powder.

The results are shown in Table. No: 7 & 8

Tapped Density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by:

$D_t = M / V_t$

Where, M is the mass of powder.

V_t is the tapped volume of the powder.

The results are shown in Table. No: 7 & 8

Angle of Repose (θ)

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder.

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$\tan(\theta) = h / r$

$\theta = \tan^{-1} (h / r)$

Where, θ is the angle of repose. h is the height in r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

The results are shown in Table. No: 7 & 8.

Table No. 1: Standard Angle of Repose as per Powder Flow Properties

S. No.	Angle of Repose (°)	Type of Flow
1	< 20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	> 34	Very Poor

Carr's index (or) % compressibility

It indicates powder flow properties. It is expressed in percentage and is give

$$\text{C. I.} = \frac{D_t - D_b}{D_t} \times 100$$

Where, D_t is the tapped density of the powder and

D_b is the bulk density of the powder.

The results are shown in Table. No: 7 & 8

Table No. 2 : Relationship between % compressibility and flow ability.

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair Passable
23 – 35	Poor
33 – 38	Very Poor
< 40	Very very Poor

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, Dt is the tapped density.

D_b is the bulk density.

If Hausner ratio <1.25 indicates better flow properties than higher ones >1.25.

The results are shown in Table. No: 7 & 8.

Tablet Manufacturing

Table No. 3: Formulation of Prasugrel hydrochloride Tablet

Batch. No	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Ingredient	mg/tablet					
Prasugrel hydrochloride	5	5	5	5	5	5
Mannitol	12	8	12	8	9	9
MCC pH-102	215	215	215	215	215	206
Croscarmellose Sodium	3	6	-	-	3	6
Cross Povidone	-	-	3	6	3	6
Sodium Starch Glycolate	3	6	3	6	3	6
Talc	8	8	8	8	8	8
Magnesium stearate	2	2	2	2	2	2
Aspartame	2	2	2	2	2	2
Total	250					

POST COMPRESSION PARAMETERS[12-16]

a) Shape of Tablet

Directly compressed tablets were examined under the magnifying lens for the shape of the tablet.

b) Tablet Dimensions

Thickness and diameter were measured using a calibrated Vernier calipers. Five tablets of each formulation were picked randomly and thickness and diameter was measured individually.

The results are shown in Table. No: 9.

c) Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Five tablets were randomly picked and hardness of the tablets was determined.

The results are shown in Table. No: 9.

d) Friability test

The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (Wt) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (WF). The % friability was then calculated by-

$$\%F = \frac{W\ (initial)-W\ (final)}{W\ (initial)} \times 100$$

The results are shown in Table. No: 9.

e) Weight Variation Test

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to U.S. Pharmacopoeia. The following percentage deviation in weight variation was allowed.

Table No. 4: Weight variation parameters

Average weight of a tablet	Percentage deviation
130 mg or less	± 10
>130 mg and <324 mg	± 7.5
324mg or more	± 5

In all the formulations, the tablet weight is 1045mg to 1145mg, hence ± 3% maximum difference allowed. The results are shown in Table. No: 9.

EVALUATION OF TABLETS[17-18]

Thickness

The thickness of the tablets was determined by Vernier calipers. Five tablets from each batch were used and the average values were calculated. The results are shown in Table. No: 9.

Hardness test

The Hardness of the tablet was measured using Tab-Machine hardness tester.

The results are shown in Table. No: 9.

Uniformity of weight (weight variation test)

This is an important in-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight. 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (± 3%). The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual Weight} - \text{Average Weight}}{\text{Average weight}} \times 100$$

The results are shown in Table. No: The results are shown in Table. No: 9.

Disintegration test

The disintegration time for immediate release layer was determined using the disintegration apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000 ml of purified water maintained at 37 ± 20 C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

The results are shown in Table. No: 9.

***In - Vitro* drug release study**

Standard USP apparatus have been used to study in vitro release profile using rotating paddle. In-vitro release rate study of immediate release tablets of Prasugrel hydrochloride were carried out using 900ml of phosphate buffer pH6.8, at 37±0.50c at 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 15, 20 & 30 min and withdrawn volume was replaced with fresh dissolution media. The withdrawn samples were diluted with dissolution medium and then filtered with whattman filter paper and assayed at 249 nm. The results are shown in Table. No: 10 & 11.

STABILITY STUDIES[19-21]

Stability testing forms an integral part of formulation development. It is important to assess the effect of temperature and humidity on stability of drug and in-vitro drug release rate. It helps to generate information for predicting the shelf life of the product and recommended storage conditions. Stability data is required to be submitted as part of the dossier submitted to the regulatory agencies.

Protocol For stability studies

Formulation was selected on the basis of in-vitro drug release profile which was comparable to that of the IR formulation under reference i.e. optimized formula for both Prasugrel hydrochloride batches.

Table No: 5 Stability Condition For Prasugrel hydrochloride Tablet

Study	Storage condition	Time Period Covered
Room Temperature (RT)	25°C ± 2°C/60%RH± 5%RH	1 months **Testing:** If accelerated condition tablet is passed
Accelerated	40°C ± 2°C/75%RH± 5%RH	1 months **Testing:** 1,2,3month

These were evaluated for their physicochemical characteristics, drug content, assay and in-vitro release profile of Prasugrel hydrochloride Tablet. In–vitro release and content of active ingredients was estimated at one month interval during to rage period. The result are shown in the table. No: 12.

RESULTS AND DISCUSSION

Table no 6: Standard Calibration Curve of Prasugrel hydrochloride

S.No	Concentration (µg/ml)	Area
1	1	0.112
2	2	0.21
3	3	0.312
4	4	0.402
5	5	0.512
6	6	0.614
7	7	0.712
8	8	0.811
9	9	0.913
10	10	0.99

*Mean±SD n=3

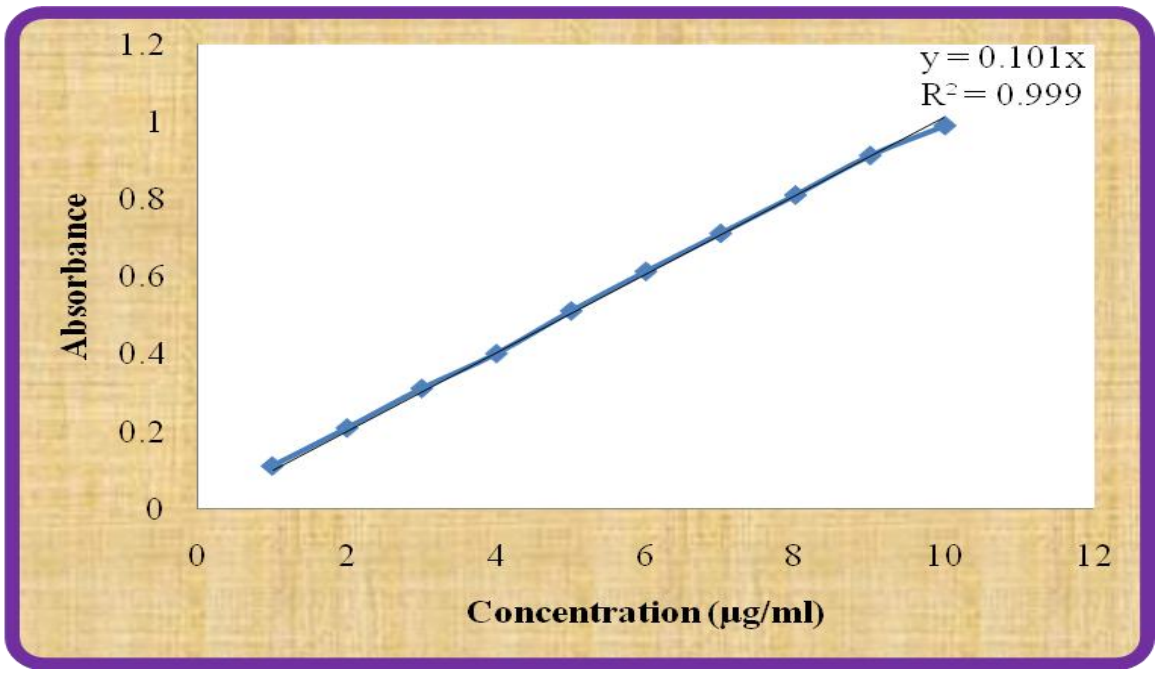

Fig. no:1 Standard Calibration Curve of Prasugrel hydrochloride

FT-IR SPECTROSCOPY

The result of FT-IR study for Prasugrel hydrochloride and their excipients are shown in Figure. No: 7 -16

FOR PRASUGREL HYDROCHLORIDE

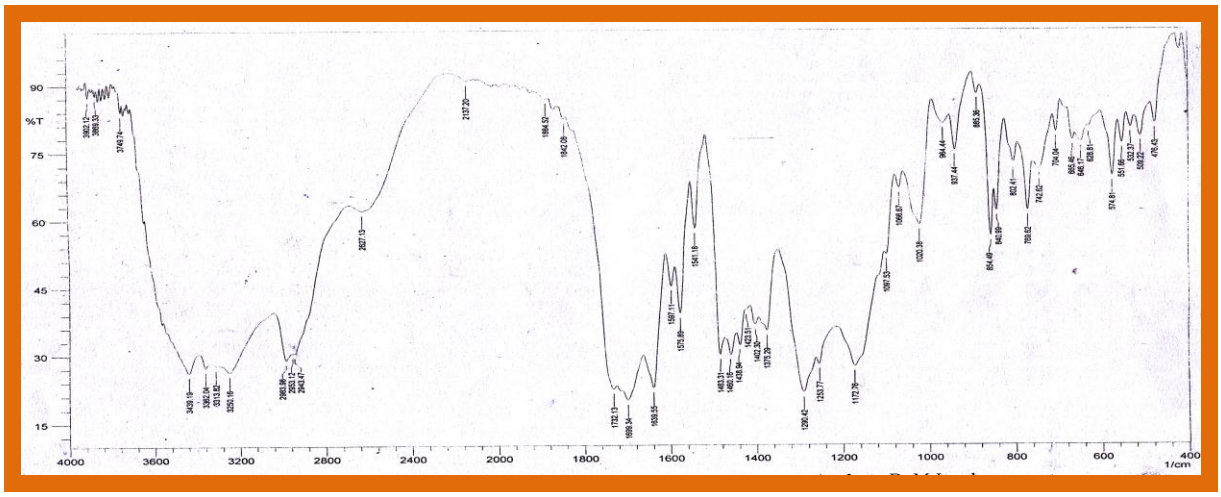

Figure No. 2: FTIR Spectrum of Pure Prasugrel hydrochloride

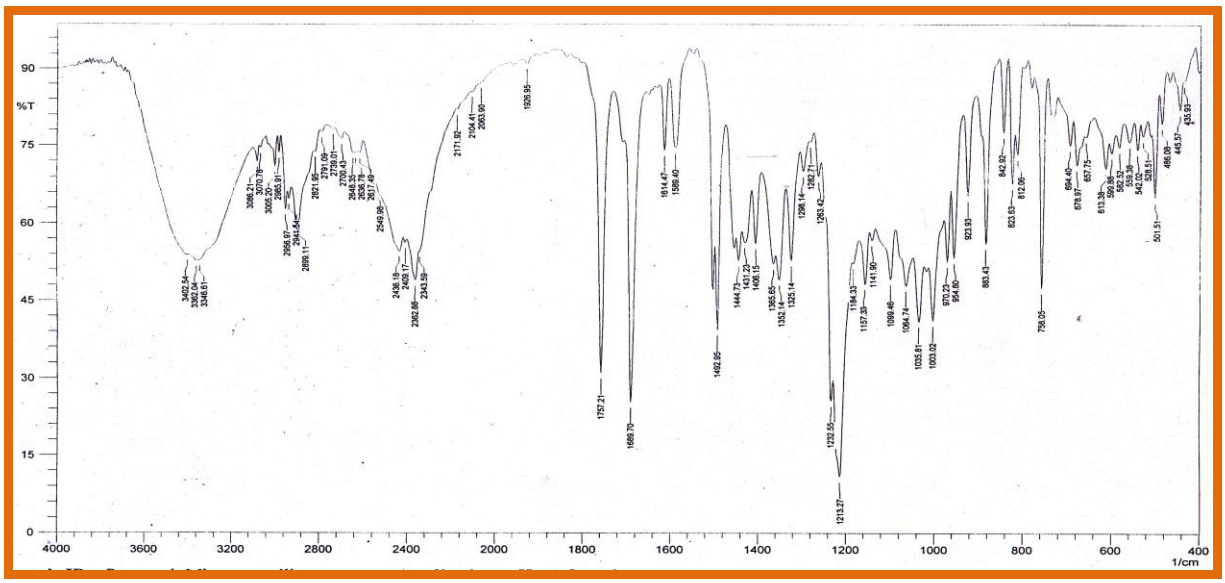

Figure No. 3: FTIR Spectrum of Prasugrel hydrochloride + MCC pH-102

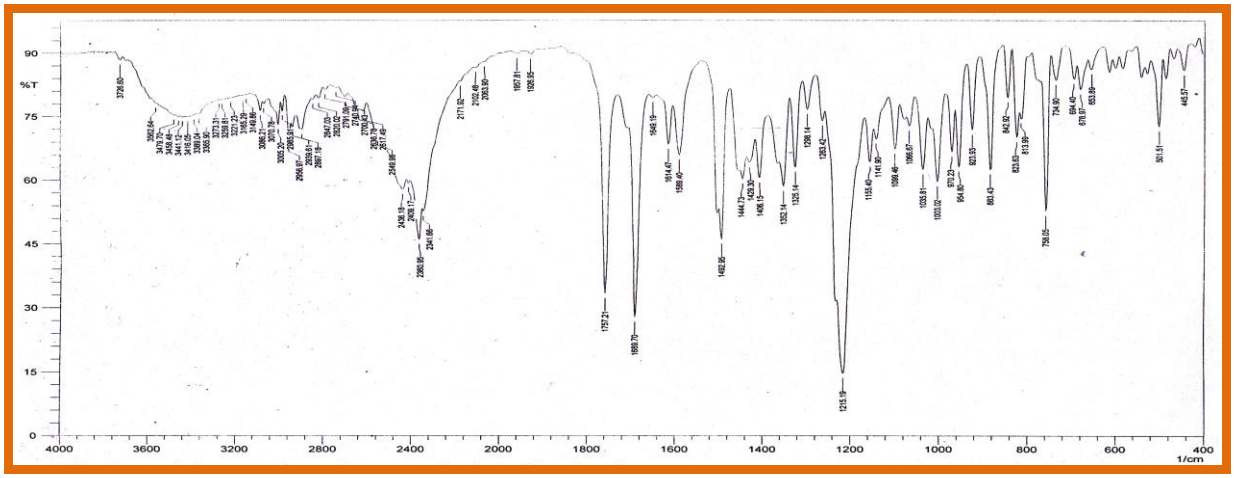

Figure.No:4 FTIR Spectrum of Prasugrel hydrochloride+Croscarmellose Sodium

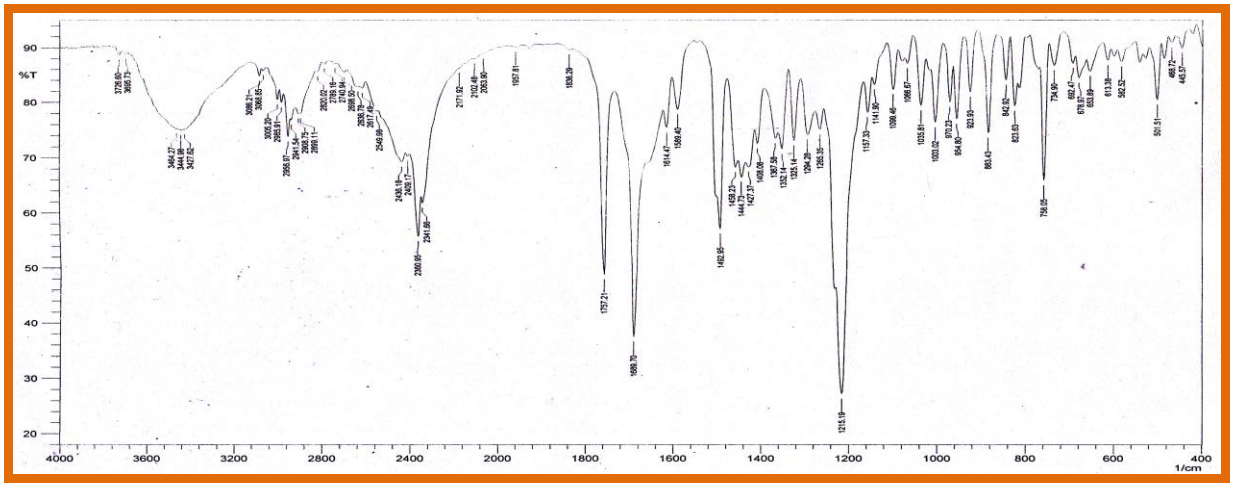

Figure.No: 5 FTIR Spectrum of Prasugrel hydrochloride + Cross povidone

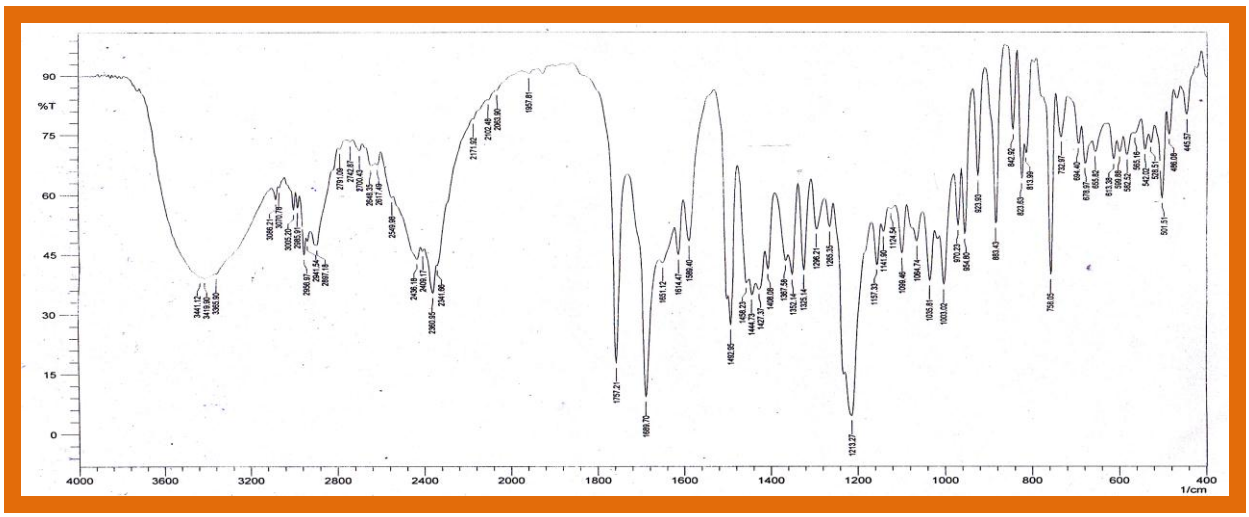

Figure.No:6 FTIR Spectrum of Prasugrel hydrochloride + All excipients

Preformulation Studies of pure drug and excipients

Table No 7: Preformulation Study of Pure Drug (PRASUGREL HYDROCHLORIDE)

S.NO.	Parameters	Result	Conclusion
1	Bulk Density*	0.675 gm/ml	------
2	Tapped Density*	0.75 gm/ml	-----
3	Angle of Repose*	19.61	Excellent
4	Carr's Index*	10 %	Excellent Flow
5	Hausner Ratio*	1.11	Better Flow
6	Melting Point*	159.2-160.7 °C	----
7	Solubility*	Freely soluble in methanol, slightly soluble in ethanol, very slightly soluble in water	

*Mean±SD (n=6)

Table No. 8: Preformulation Study of the blend (Prasugrel hydrochloride)

Batch Code	Bulk Density*	Tapped Density*	Angle of repose*	% Compressibility*	Hausner Ratio*	Loss on Drying*
F1	0.41	0.47	24.58	12.76	1.15	2.1
F2	0.44	0.52	25.91	15.38	1.18	1.9
F3	0.44	0.51	26.86	13.72	1.16	1.8
F4	0.47	0.54	24.43	12.96	1.14	1.7
F5	0.45	0.50	24.10	12.00	1.06	1.6
F6	0.47	0.52	25.42	9.61	1.11	1.5

*Mean±SD (n=6)

The physical parameters of drug as well as blends concluded that these were considerably good to formulate the tablet using direct compression technique.

Table No 9: Evaluation of Prasugrel hydrochloride IR Tablets

Batch No	Weight variation (mm)**	Diameter (mm)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)*	Disintegration Time*
F1	252±6.5	5.39±0.02	3.32±0.03	3.45±0.21	0.25	53 seconds
F2	251±6.5	5.28±0.01	323±0.04	3.51±0.20	0.31	47 seconds
F3	253±5.6	5.39±0.03	3.34±0.04	3.45±0.14	0.28	49 seconds
F4	251±6.5	5.47±0.02	3.25±0.05	3.57±0.13	0.32	51 seconds
F5	250±5.8	5.38±0.03	3.36±0.04	3.67±0.12	0.34	48 seconds
F6	251±6.8	5.49±0.01	3.25±0.06	3.87±0.15	0.35	51 seconds

*Mean±SD (n=6) **Mean±SD (n=20)

Table.No:10 Dissolution Profile of the Prasugrel hydrochloride IR Tablets F1-F6

% Cumulative Amount of Drug Release						
Time (Minutes)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
5	58.34	59.13	60.54	59.78	60.67	65.19
10	78.98	79.45	80.56	79.67	80.19	84.12
15	92.14	94.45	95.19	91.78	93.18	97.01
20	93.45	95.76	96.87	93.17	95.48	100.17
30	97.45	98.13	98.78	96.67	97.87	103.12

*Mean±SD (n=6)

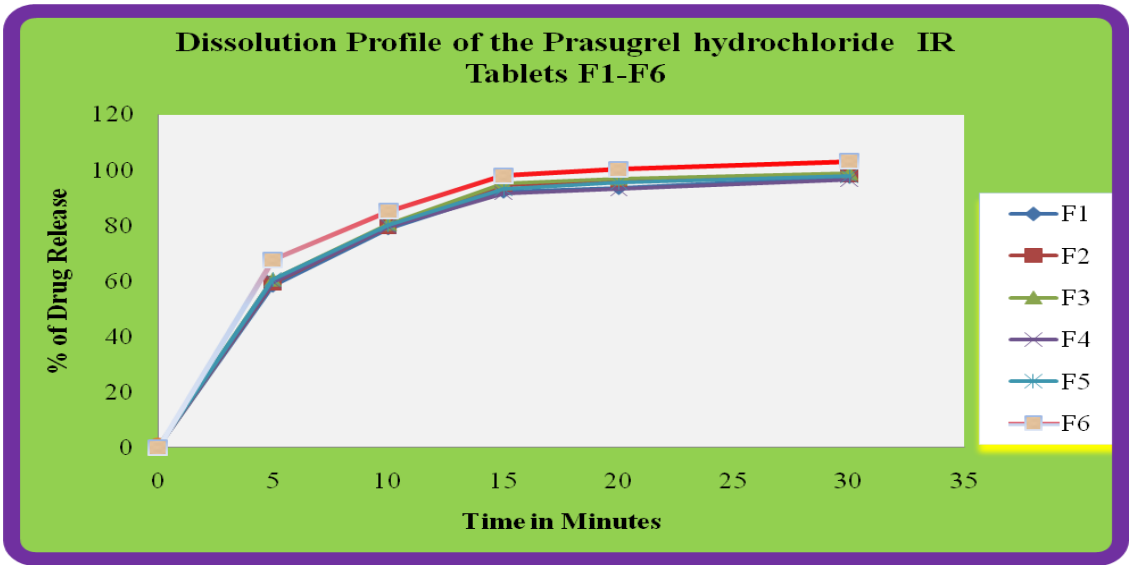

Figure.No:7 Dissolution Profile of the Prasugrel hydrochloride IR Tablets F1-F6

Table No 11: Dissolution Profile of the Prasugrel hydrochloride IR Tablet Optimized Formulation F6 with Innovator Tablet

% Cumulative Amount of Drug Release		
Time in (Minutes)	**F6**	**INNOVATOR**
5	65.19	68.4
10	84.12	85.7
15	97.01	98.8
20	100.17	99.8
30	103.12	101.30

*Mean±SD (n=6)

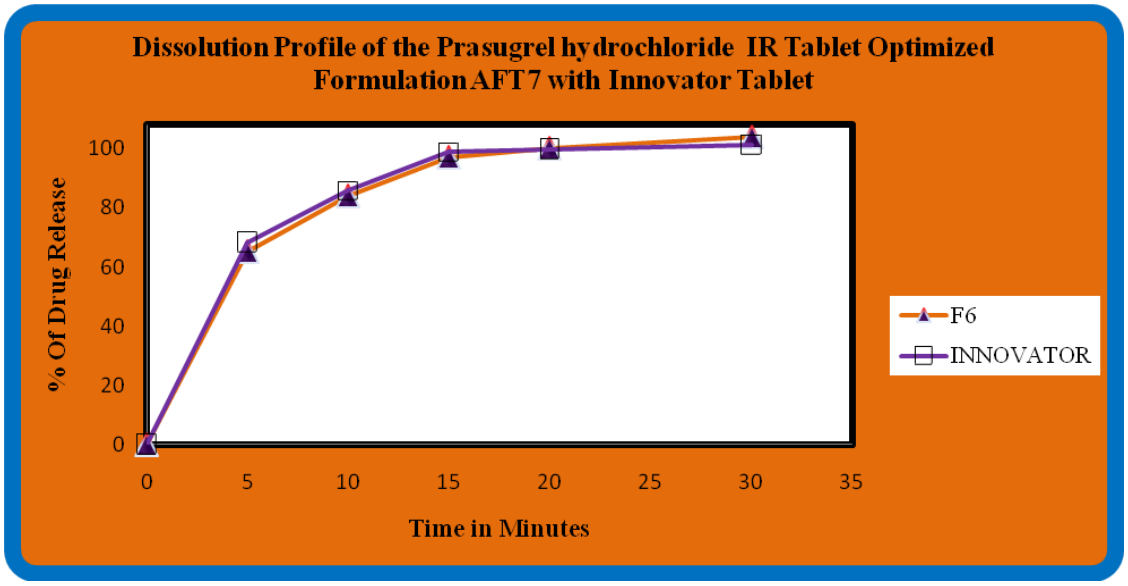

Figure No: 8 Dissolution Profile of the Prasugrel hydrochloride IR Tablet Optimized Formulation F6 with Innovator Tablet

STABILITY STUDIES

Table No. 12: Stability Studies Data of the Prasugrel hydrochloride Optimized Formulations (F6)

Parameters	Initial	1st Month	
		RT	40°C
Weight variation (mm)**	251±6.8	251±5.8	250.5±7.6
Diameter (mm)*	5.69±0.03	5.68±0.03	5.67±0.03
Thickness (mm)*	3.45±0.06	3.44±0.06	3.45±0.06
Hardness (kg/cm2)*	3.87±0.15	3.86±0.15	3.86±0.14
Disintegration Time*	1 mts 12 sec	1 mts 12 sec	1 mts 11 sec

*Mean±SD (n=6) **Mean±SD(n=20)

SUMMARY AND CONCLUSION

The research work was aimed with formulation and evaluation of immediate release tablets of prasugrel hydrochloride as combinational cardiovascular complication. The drug powders were subjected to Preformulation studies. The Preformulation characteristics are within the Pharmacopeial specifications.

The bulk density of the powdered blend was found to be 0.41 - 0.47 gm/cm^3, tapped density between 0.47 – 0.54gm/cm^3 for all formulations. % Compressibility, Hausner ratio to be found between USP limit. Angle of Repose was found in the range of 28º. The flow properties of the powdered blend for all the batches were found to be good and free flowing. The weight variation, hardness and friability of all the formulated tablets within the specified requirements. The disintegration times for the formulated tablets are within the range of USP. For Prasugrel hydrochloride IR tablets direct granulation was method of choice. Optimization was done and it was found that release profile was found to be best with two super disintegrants i.e. Croscarmellose sodium and Crospovidone.

This results, it can be concluded that drug release profile of batch .no: F1 to F6, the optimized batch (F6) was selected based on the drug release profile. The mixture of Two (Croscarmellose sodium1.5% and Crospovidone3%) Super disintegrants was used for the optimized batch (F6) was compared with that of innovator product. The Percentage cumulative drug release of batch No. F6 was found at 30 Minutes was 103.12% and the innovator product was 101.30%. The stability studies of optimized formulation (F6) when it was compared with innovator product it is stable.

From the above studies; it was concluded that the immediate release F6 containing two super disintegrants (Croscarmellose sodium and Crospovidone) showed the ability to release of

drug immediate. It is used to inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established atherosclerotic disease. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function can result in the reduction of the rate of death and the rate of is chaemic cardiovascular events such as myocardial infraction or stroke.

ACKNOWLEDGEMENTS

Authors are thankful to Prof (Dr.). B. Jaykar, Principal Vinayaka Mission's College of Pharmacy, Salem, Tamil nadu and providing all the facilities for this research project.

REFERENCES

1. Remington, The Science and pharmacy practice of pharmacy, 21st edition volume I & II, Page. no: 869-870.
2. Anisul Quardir, Karl Kolter, A comparative study of current Super disintegrents, pharmaceutical technology, October 2006.
3. Bruckert E, Davidoff P, Grimaldi A; Increased Serum Levels of Lipoprotein (a) in Diabetes Mellitus and their Reduction with Glycemic Control. J Am Med Assoc. 1990; 263(1): 35-36
4. Bruce H R, Wolffenbuttel, Gerhard M, Dieter M. Efficacy and safety of a new cholesterol synthesis inhibitor, Atorvastatin, in comparison with simvastatin and pravastatin, in subjects with hypercholesterolemia. The Netherlands Journal of Medicine. 1998; 52(4): 131-137.
5. Swarbrick J, Boylan J.C., Encyclopedia of Pharmaceutical Technology, Second Volume-1992; 531-536.
6. Vyas S, Khar R. Targeted and Controlled drug delivery; Novel carrier systems. First edition, CBS Publishers; New Delhi; 2006; 417-457.
7. Amidon, G. E.; Augsburger, L. L.; "Physical test methods for powder flow characterization of pharmaceutical materials: a review of methods"Pharmacopeial Forum 25, 1999; 8298-8308.
8. Clarke's "Isolation and Identification of drugs", 2nd edition, The pharmaceutical press, London, 1986; 838.
9. Regmington : The Science and practice of Pharmacy. 20th Edition; 2000; 903-929.

10. Banker G.S. Anderson N.R., "Tablets" chapter 11 in "The theory and practice of industrial pharmacy" edited BY Lachman Edition, Varghese Publishing House, 1991; 296-317.
11. Fonner "Characterization of Granulation" in "Pharmaceutical dosage forms: Tablets", Volume. No:2, edited by Lieberman H.A., Lachman L., Marcel Dekker; 240-249.
12. Carver, L.D.: Particle Size Analysis, Industrial Research, August1971; 39 – 43.
13. Agbada, C.O., and P.York. "Dehydration of theophylline monohydrate powder effects of particle size and sample weight", Int. J. Pharm. 1994; 106: 33-40.
14. The United States Pharmacopoeia. The National Formulary, USP 22, NF 17, United States Pharmacopoeial Convention, Inc., Rockville, M.D., 1990; 1528.
15. Carver, L.D.: Particle Size Analysis, Industrial Research, August1971; 39 – 43.
16. Agbada, C.O., and P.York. "Dehydration of theophylline monohydrate powder effects of particle size and sample weight", Int. J. Pharm. 1994; 106: 33-40.
17. Guidance for Industry SUPAC-MR. Modified Release Solid Oral Dosage Forms Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls. In vitro Dissolution Testing and In Vivo Bioequivalence Documentation.
18. Moore, J., Flanner, H., Mathematical comparison of dissolution profiles. Pharm Tech. 20; 1996; 64-74.
19. Ahlneck, C., and Zografi. 1990. The molecular Basis of moisture effects on the physical and chemical stability of drugs in the solid state, Int. J. Pharm. 1990; 62: 87-85.
20. ICH Guideline Published by Europian Medicines agency CAMP /ICH/ 2736/99 August 2003.
21. http://www.ichguidelines.com.7