Research article Available online www.ijsrr.org ISSN: 2279–0543

International Journal of Scientific Research and Reviews

Dissolution Rate Improvement of Prasugrel Hydrochloride by Solid Dispersion Method Using HPMC-AS as a Polymer

Warkad S. S[1]*, Anantwar P. S[2], Bhusari M. R[1], Tale P. D[1] and Pakhare V. S[1]

[1]Department of pharmaceutics, MVP's college of pharmacy,Gangapur road, Nashik, Affiliated to savitribai phule pune university, pune, Maharashtra email ID :sachinwarkad95@gmail.com, Mob no:9970787103; manojbhusari5555@gmail.com, Mob no : 9527690632; priyankatale@gmail.com, Mob no: 7775829054; vaishnavi8397@gmail.com, Mob no :8856063641

[2]Shri. Saptashrungi Ayurved Mahavidyalay Hirawadi, Nashik. Affiliated to Maharashtra university of health sciences Nashik, Maharashtra, Mob no : 9423173911

http://doi.org/10.37794/IJSRR.2019.8427

ABSTRACT:

The aim of this study was Dissolution rate Improvement of Prasugrel Hydrochloride by solid dispersion technique. Prasugrel HCL is a poorly water soluble (BCS class II) antiplatelet drug. Due to poor water solubility of this drug, its bioavailability is dissolution rate limited. The purpose of the present work is to improve the dissolution rate of Prasugrel HCL in aqueous media as well as at high pH conditions by solid dispersion technique. Solid dispersions are one of the most promising strategies to improve the solubility and dissolution rate of poorly water-soluble drugs. Solid dispersion was prepared by two preferable methods (Grinding method, solvent evaporation method). HPMC-AS was used as polymer to prepare solid dispersion. HPMC-AS is an enteric polymer which is used as a carrier for Bioavailability enhancement in various solid dispersion methods. Four drug polymer ratios were selected (1:1, 1:2, 1:3, 1:4) for each method to prepare solid dispersion. Solid dispersion prepared from both the methods was further evaluated for solubility, total drug content, compatibility testing, and drug release. Solid dispersion was prepared by using (1:2) drug polymer show significant increase in solubility than the other drug polymer ratio. Above this ratio there is no significant change in solubility. In case of optimized solid dispersion, drug release was found to be higher in Grinding method (F2= Optimized batch from Grinding method and % CDR 90.9%) in 900ml of phosphate buffer pH 6.8. And optimized solid dispersion from Solvent evaporation method drug release was found to be (S2= Optimized batch from solvent evaporation method and % CDR 84.1%) in 900 ml phosphate buffer 6.8 which is less as compared with the optimized batch obtained from Grinding method.

KEYWOERDS: Prasugrel HCl, solid dispersion technique, dissolution rate, HPMC-AS, Grinding method.

***Corresponding author**

Mr. Sachin S. Warkad

Research scholar, Department of Pharmaceutics,
MVP Samaj's college of pharmacy,
Gangapur road, Nashik, Maharashtra-422002
Email Id- sachinwarkad95@gmail.com
Contact no. 9970787103/8888515780

1. INTRODUCTION[1,2,3,4,5]

Acute coronary syndrome:

Acute coronary syndromes are conditions characterized by the sudden onset of coronary insufficiency as a result of thrombotic occlusion of one or more coronary arteries. Acute coronary syndrome is a major cause of morbidity and mortality. Arterial thrombosis after coronary artery plaque rupture is the proposed most common mechanism for ACS, and platelet activation, adhesion, and aggregation play central roles in its development. Haemostas is consists of a complex interplay of the vascular endothelium, platelets and coagulation factors. This process can lead to clot formation in the arteries or veins, which ultimately manifests as an acute coronary syndrome or venous thrombolism. As such, antithrombotic drugs, including antiplatelet therapies and anticoagulants, are frequently used in patients with cardiovascular disease. Platelets play a central role in the pathogenesis of a the rothrombos is and in the formation of thrombi following coronary angioplasty, with and without stent implantation. Platelets initially adhere at sites of vascular injury, atherosclerotic plaque rupture, balloon angioplasty, and stenting. Platelet activation following these interactions results in the release of ADP promotes platelet activation via the G-protein linked P2Y1 and P2Y12 purinergic receptors leading to further platelet activation, aggregation, and other platelet functions, Such as platelet shape change, secretion and the development of pro-coagulant and pro-inflammatory activities. Activated platelets are recruited to sites of coronary plaque rupture and intraarterial stenting, thereby forming aggregates that may lead to platelet rich thrombi, vascular occlusion, tissue ischemia, and myocardial necrosis in what is collectively known as Acute coronary syndrome (ACS). The term ACS is a pathophysiological continuum progressing from ischemic chest pain with sudden onset and worsening, to ischemia severe enough to cause irreversible myocardial damage detected with cardiac biomarkers without persistent ST-segment elevation, to total occlusion of the culprit coronary artery with persistent ST-segment elevation, resulting in myocardial necrosis and elevated biomarkers. ACS occurs in a diverse global population and has a significant socioeconomic impact as patients require hospitalization, rehabilitation, and often suffer subsequent ischemic events. Acute coronary syndromes will likely remain one of the causes of hospitalization worldwide due to the increasing prevalence of risk factors for coronary heart disease and the increasing size of the aged population.

Prasugrel as an Antiplatelet Agent:

Prasugrel is a novel antiplatelet prodrug belongs from the thienopyridine class which is approved by the united states food and drug administration on July 10, 2009 for the treatment of patients with acute coronary syndrome who are undergoing percutaneous coronary intervention. As

Prasugrel is a prodrug it requires conversion to its active metabolite for therapeutic effect. Antiplatelet agents are drugs that inhibit enzymes or receptors required for platelet activation, aggregation and thrombus formation. Antiplatelet drugs protect against myocardial infarction, stroke, cardiovascular death, ischemia and other serious vascular events in patients with a history of previous vascular events or known risk factors for cardiovascular disease.

Prasugrel HCL is a poorly soluble (BCS Class II) drug used for the treatment of Acute coronary syndrome. Due to poor water solubility of this drug, its bioavailability is dissolution rate limited. Prasugrel HCL is 3rd generation thienopyridine which is an antiplatelet drug, recently approved for prevention of thrombotic cardiovascular complications in patients with an acute coronary syndrome and in patients who are managed with percutaneous coronary intervention. Prasugrel HCL is a BCS Class II drug which is soluble to slightly soluble at pH 1-4, very slightly soluble at pH 5, practically insoluble at pH 6-7 and water. During ACS an antiplatelet drug should show quick and high oral bioavailability which can be achieved by high aqueous solubility. The oral bioavailability of Prasugrel HCL is (~79%) but it may vary due to its disparity in its solubility.

Solid Dispersion as a dosage type has been established a superior choice for the compounds having poor aqueous solubility. Solid dispersions in water-soluble carriers have caught right interest as a method of enhancing the dissolution rate and bioavailability of hydrophobic compounds. Though solid dispersions have large potential for enhancing drug solubility. There are numerous methods accessible to boost the solubility of the new drug during which solid dispersion emerged promising. Solid dispersion systems can increase dissolution rate and bioavailability of water insoluble compounds as when these are exposed to aqueous media, the carrier dissolves, and also the drug is released as fine particles. This greatly reduces particle size and increases surface area, which results in improved dissolution rates and absorption.

Advantages of Solid Dispersions

The major advantage of solid dispersions is that it improves the dissolvability of a poorly water soluble drug in a pharmaceutical composition and end up in speedy dissolution rates thereby enhancing the bioavailability of compound. In conjunction with this approach may additionally supply alternative benefits are,

1. Speedy disintegration of oral tablets.
2. As a formulation vehicle.
3. Particles with reduced particle size.
4. Particles with improved wettability.

5. Particles with higher porosity.

6. Compounds in amorphous state.

Disadvantages of Solid Dispersions

Moreover, most of the polymers used in solid dispersions can absorb moisture, which can end in section separation, crystal growth or conversion from the amorphous to the crystalline state or form a metastable crystalline form to a more stable structure during storage.

2. MATERIAL AND METHOD

Prasugrel HCL was obtained from Amneal Pharmaceutical, Ahmedabad HPMC-AS was obtained as gift sample from Glenmark pharmaceutical Ltd. Mumbai.

Preparation of Solid Dispersion

Solid dispersion was prepared by two preferable methods.

Grinding Method

With the help of Grinding Technique for preparing solid dispersion taking a carrier material and a drug with the quantities relation of 1:1-1:4 was mixed uniformly, by putting them in a mortar, after that the blend was taken out, and screened through an 80 mesh sieve.

Solvent evaporation Technique Solvent Technique for preparing a solid dispersion during which physical mixture of the drug and carrier material was dissolved in a very common solventi.e.Acetone, which is stirred continuously for uniform distribution of drug in carrier material and evaporated until clear, solvent free film is left. The film was additionally dried to constant weight.Four batches were taken, having weight ratio (1:1, 1:2, 1:3, 1:4) for each method.

3. EVALUATION

3.1. Solubility (S)

For the determination of Prasugrel HCL (Solid dispersion) solubility, in various solvents (Distilled water, 0.1N HCL, Phosphate buffer-pH 6.8) an excess amount of solid dispersion containing Prasugrel HCL was placed in glass bottles containing 10ml of solvent. The bottles were kept for 24hrs at room temperature. The supernatant was taken and analyzed by using UV spectrophotometer at respective wavelength of maximum absorption in respective solvents. The solubility values found by solid dispersion prepared by grinding method and solid dispersion method are given in table 9.13, 9.14 respectively.

3.2. Determination of Drug content in Drug: Polymer solid Dispersion (15)

The drug content was determined by using UV Analysis.

From Standard curve of Prasugrel HCL total Prasugrel HCL content was determined. The drug content was calculated by dissolving Solid Dispersions equivalent to 10mg drug into a 100 ml volumetric flask and dissolved in minimum amount of phosphate buffer pH 6.8 . And the volume was made upto the mark using phosphate buffer pH 6.8 and filtered through 0.45µ filter and assay for drug content using UV double beam spectrophotometer at 254nm. Three replicates were prepared, and the average drug contents were estimated in the prepared solid dispersion. Actual drug content was calculated for all batches using the equation:

Drug content (%) = Gact/Gsd x 100

Where Gact is Actual Prasugrel HCL content in weighed quantity of solid dispersion, and Gsd is theoretical amount of Prasugrel HCL in SD.

3.3. XRD Analysis:

XRD Analysis is used to find out any changes in the crystallinity of the drug which precipitated in amorphous form, when formulated into a solid dispersion. Powder XRD is used to study any changes in crystallinity of the drug which could be one of the mechanisms responsible for the improved dissolution

3.4. Dissolution study (In-Vitro drug Release)

In-Vitro release of Prasugrel HCL from solid dispersion was studied using USP dissolution apparatus I (Lab-India Disso 8000). The amount of solid dispersion equivalent to 10 mg of Prasugrel HCL Was taken into the muslin cloth and each formulation was exposed to dissolution medium (Phosphate buffer 6.8) maintained at 37± 0.5°C stirred at 50 rpm for 30 min. 5 ml of aliquots withdrawn from the vessel at time interval of (05, 10, 15, 20, 25, 30min.) and replaced with 5ml of fresh dissolution medium after each sampling to maintain the constant volume (sink conditions). The withdrawn samples were analyzed by UV-spectrophotometer at 257nm. Prasugrel HCL concentration was calculated and expressed as percentage of Prasugrel HCL dissolved. Results obtained by solid dispersion prepared by grinding method and solvent evaporation method are shown in table no 9.15, 9.16 respectively. And comparison of dissolution profile of optimized batches from both the methods is shown in table no 9.17.

Table No: 1. Dissolution study parameter.

Sr.no	Parameter	Specification
1	Dissolution apparatus	USP I
2	Dissolution medium	Phosphate buffer 6.8
3	Volume	900 ml
4	Temperature	37± 0.5°c
5	Rotation speed	50 RPM
6	Λmax	254 nm

4. RESULT AND DISCUSSION

4.1. Preliminary characterization:

Identification of drug

a. Drug sample and polymer procured were studied for organoleptic properties such as colour, odour and appearance. The results are shown below.

1. Drug

Table no: 2. Organoleptic properties of Drug.

Sr.no	Parameter	Reported standard	Observed standard
1	Colour	White crystalline solid	White crystalline solid
2	Odour	Odourless	Odourless
3	Appearance	Crystalline	Crystalline

2. Polymer

Table No 3. Organoleptic properties of polymer

Sr.no	Parameter	Reported Standard	Observed Standard
1	Colour	White –off white	White –off white
2	Odour	Odourless	Odourless
3	Appearance	Powder	Powder

4.2. Melting point

Table no 4. Melting Point

Sr. no.	Parameter(Melting Point °C)	Reported Standard	Observed Standard
1	Drug	185^0C-187^0C	185^0C-187^0C
2	Polymer	65^0C-67^0C	65^0C-67^0C

4.3. Determination of solubility:

The solubility of Prasugrel HCL was studied in different solvents like water, Phosphate buffer pH 6.8, 0.1N HCL.

Table no 5. Determination of Solubility.

Solvent	**Prasugrel HCL (mg/ml)**
Distilled water	0.0020
Phosphate buffer pH 6.8	0.0024
0.1N HCL	0.0513

4.4. Determination of wavelength maxima for Prasugrel Hydrochloride

The maximum absorption value of pure drug Prasugrel hydrochloride in methanol was found at 252nm. Therefore, 252nm were recorded as λmax of the pure drug Prasugrel hydrochloride. The observed λmax value of drug was found to be similar as given in literature. Hence the drug was considered to be pure.

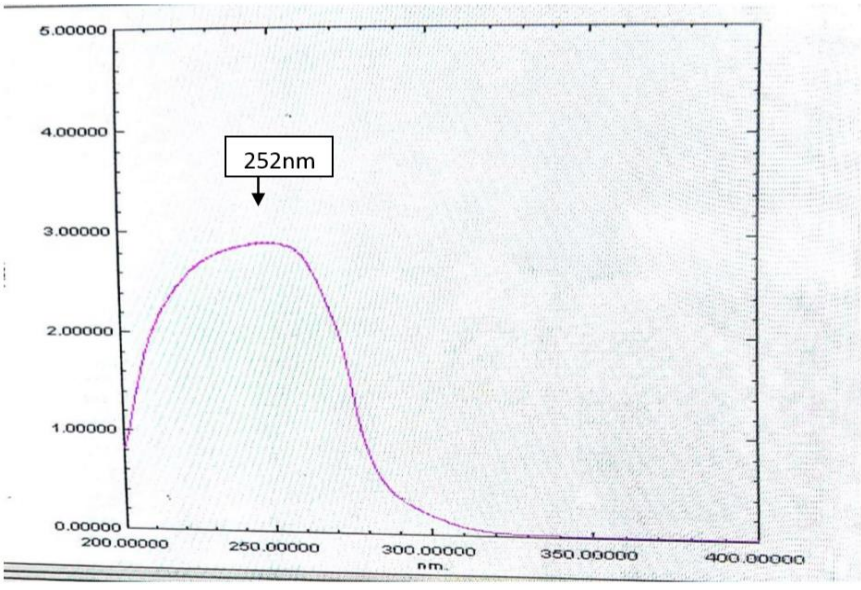


Figure No.1 UV Spectrum of Prasugrel HCL in Methanol.

4.5.Construction of Calibration curve (Beer-Lambert's plot) of Prasugrel HCL.

Calibration curve of Prasugrel HCL in water Concentration and Absorbance values for Prasugrel HCL in Water. (λmax- 254nm)

Table No 6. Concentration and Absorbance values for Prasugrel HCL in Water.

Sr. no.	Concentration (ppm)	Absorbance
1	10	0.081
2	20	0.172
3	30	0.243
4	40	0.318
5	50	0.407
6	60	0.492

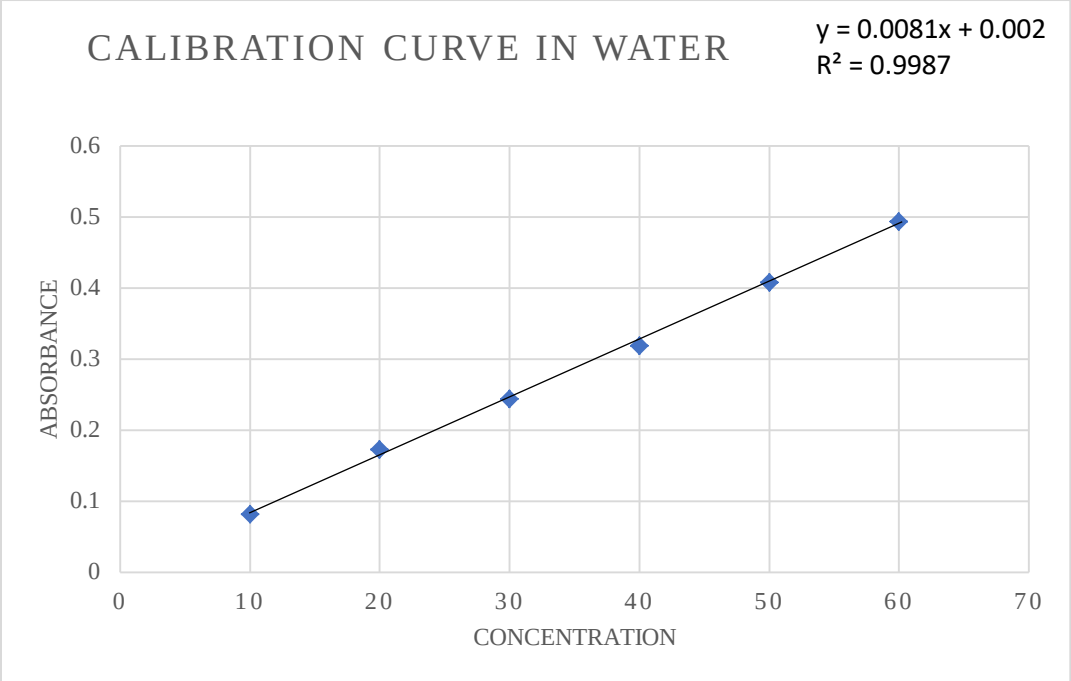


Figure No.2 Calibration curve of Prasugrel HCL in Water.

4.6. Calibration curve (Beer-Lamberts plot) of Prasugrel HCL in 0.1N HCL

Concentration and Absorbance values for Prasugrel HCL IN 0.1N HCL (λmax- 254nm)

Table No 7.Concentration and Absorbance values for Prasugrel HCL IN 0.1N HCL

Sr no	**Concentration(ppm)**	**Absorbance**
1	10	0.168
2	20	0.248
3	30	0.337
4	40	0.432
5	50	0.522
6	60	0.627

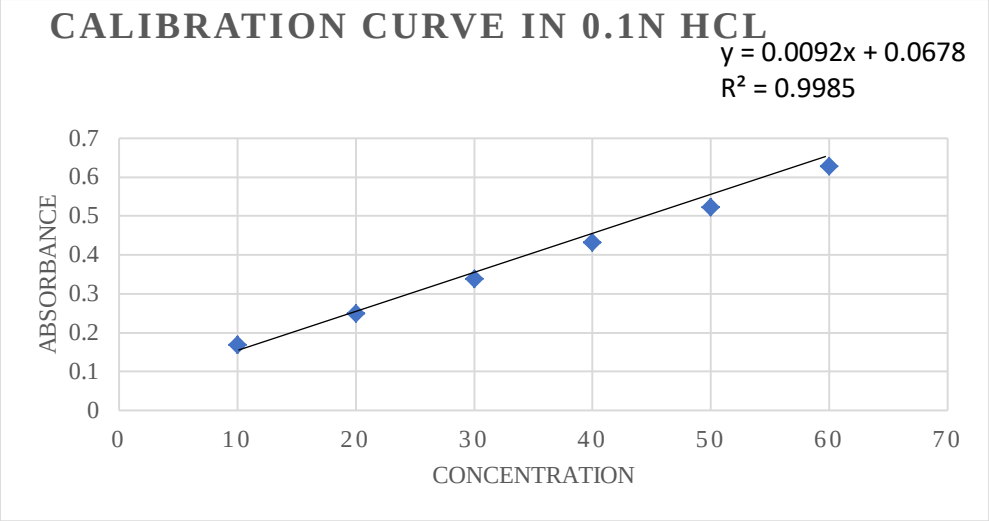


Figure No 3 Calibration curve of Prasugrel HCL in 0.1N HCL

4.7. Calibration curve (Beer-Lamberts plot) of Prasugrel HCL in phosphate buffer

Concentration and Absorbance values for Prasugrel HCL in phosphate buffer 6.8 (λmax- 254nm)

Table No 8. Concentration and Absorbance values for Prasugrel HCL in phosphate Buffer 6.8.

Sr. no.	Concentration(ppm)	Absorbance
1	10	0.082
2	20	0.171
3	30	0.244
4	40	0.316
5	50	0.405
6	60	0.496

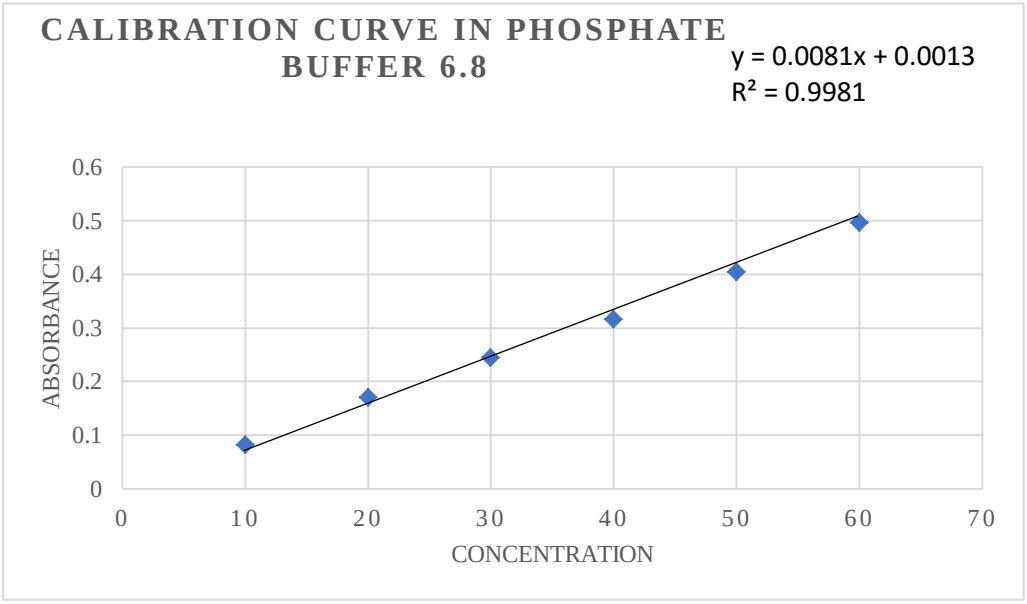


Figure No. 4 Calibration curve in Phosphate buffer 6.8

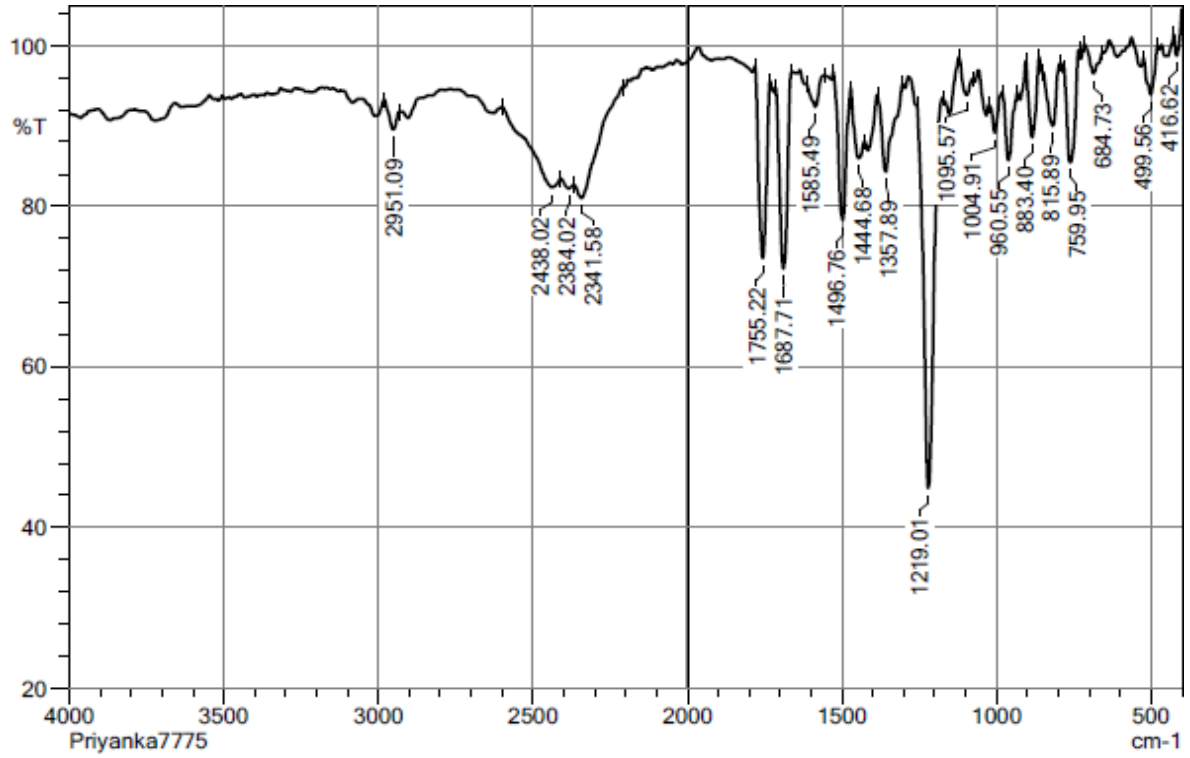


Figure No. 5 ATR spectra of Prasugrel HCL

4.8. ***Fourier Transform Infrared Spectroscopy (FTIR)*** FTIR spectra of Prasugrel HCL and HPMC-AS showed all the peaks corresponding to the functional groups present in the structures and thus identification of Prasugrel HCL and HPMC- AS was confirmed.

Values of major peaks in ATR spectrum of Prasugrel hydrochloride.

Table No 9. Values of major peaks in ATR spectrum of Prasugrel hydrochloride

Frequency (cm^{-1})	**Functional Group**	**Standard Value**
1755.22	C=O (Aliphatic ester)	1750-1735 cm^{-1}
1687.71	C=O stretch(ketone)	1695-1680 cm^{-1}
1496.76	C=C Aromatic stretch	1600-1475 cm^{-1}
1219.01	C-N stretch(Aromatic amine)	1350-1250 cm^{-1}
759.95	C-H Aromaticstretch (Assymmetricstretch)	900-690 cm^{-1}
1375.89	C-F stretch	1400-1000 cm^{-1}

4.9. FTTR spectra of HPMC-AS

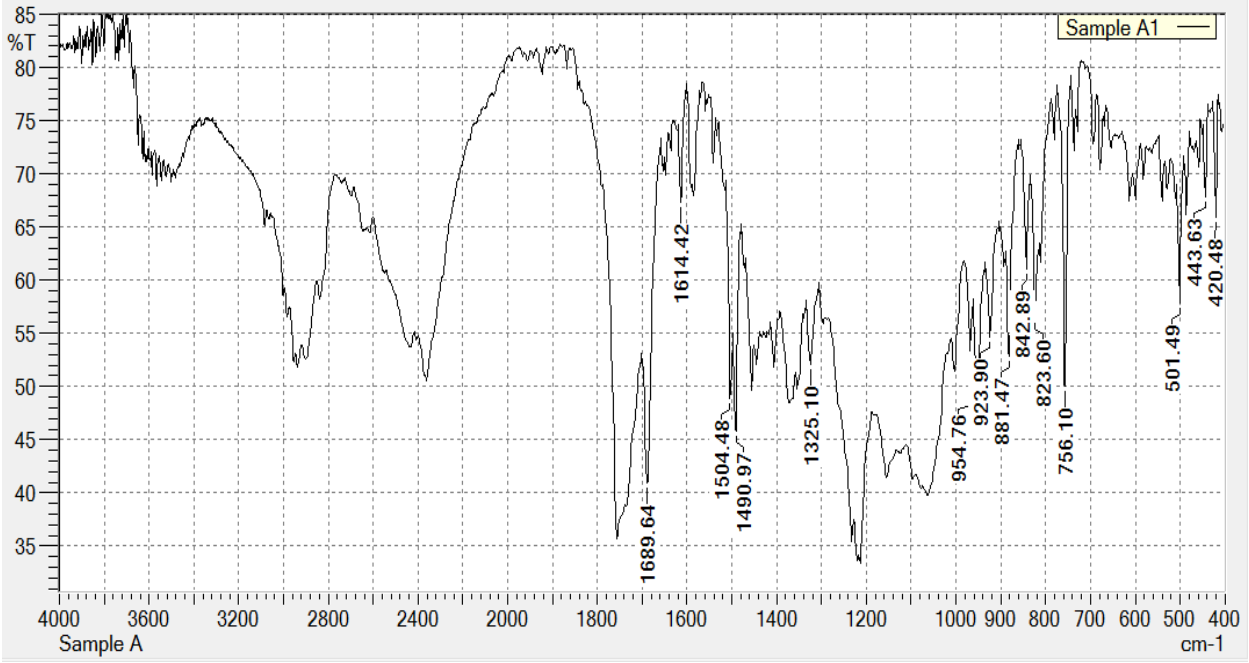


Figure No 6 FTTR spectra of HPMC-AS

Table No 10.Values of major peaks in FTIR spectrum of HPMC-AS.

Functional group	Frequency(cm^{-1})	Standard value
C-O(Ether)	1325.10	1300-1000
C=O (Ester)	1689.64	1750-1735
C-H (Alkane)	1490	1465
C=O (Acid)	1750	1700-1725
OH (acid)	3090	2400-3400

4.10. FTIR Spectra of physical mixture of Prasugrel HCL and HPMC-AS

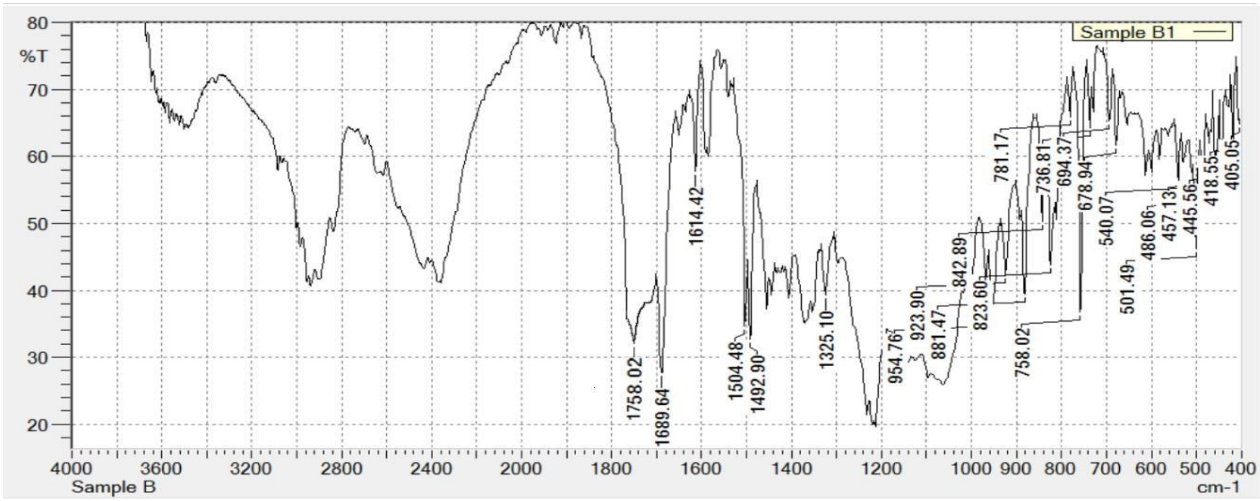


Figure No 7. FTIR Spectra of physical mixture of Prasugrel HCL and HPMC-AS

Table No 11. Values of major peaks in FTIR spectrum of solid Dispersion

Frequency	Functional group	Standard value
1758.02	C=O (Aliphatic ester)	1750-1735 cm^{-1}
1689.64	C=O stretch (Ketone)	1695-1680 cm^{-1}
1492.90	C=C Aromatic	1600-1475 cm^{-1}
1325.10	C-F Stretch	1400-1000 cm^{-1}
758.02	C-H Aromatic stretch	900-690 cm^{-1}

The Characteristic peaks of Prasugrel HCL appeared in the spectrum of solid dispersion without any significant change in the position. It indicates that there was no any interaction between drug and polymer.

4.11. DSC Analysis

Thermal behavior of pure drug and corresponding drug dispersion system are depicted in Fig. 9.8, 9.9, 9.10. The pure Prasugrel HCL shows a sharp endothermic peak at 186°C. The characteristic endothermic peak corresponding to melting peak of pure Prasugrel HCL was shifted towards lower temperature, with reduced intensity in solid dispersion prepared by grinding method. This could be attributed to higher polymer concentration and uniform distribution of Prasugrel Hydrochloride in the crust of polymer, resulting in complete miscibility of molten drug inpolymer.

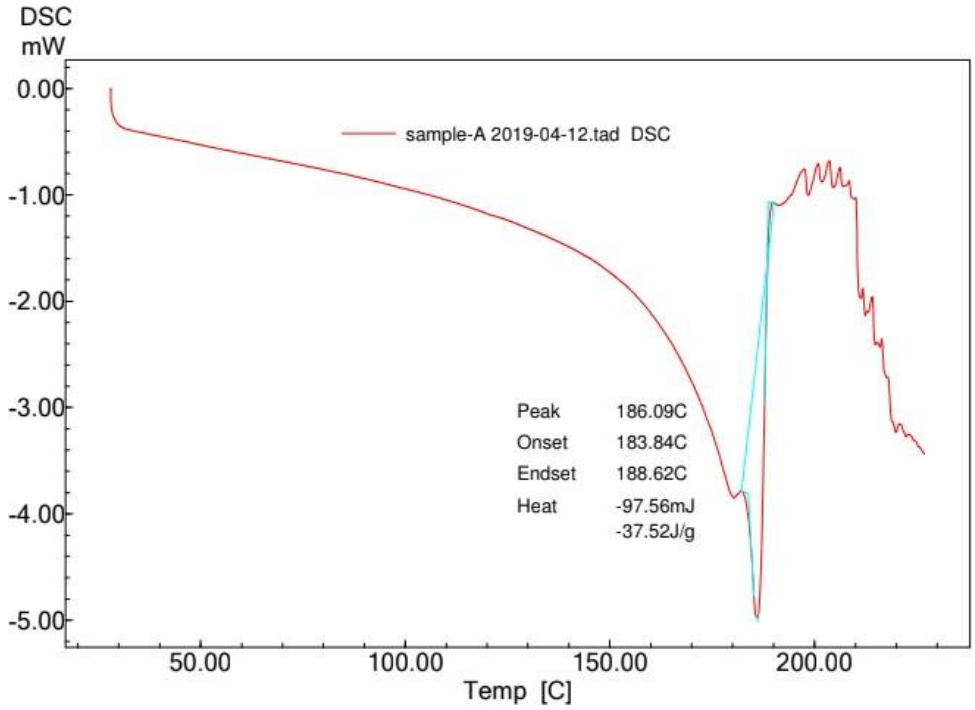


Figure No 8 DSC of Prasugrel HCL

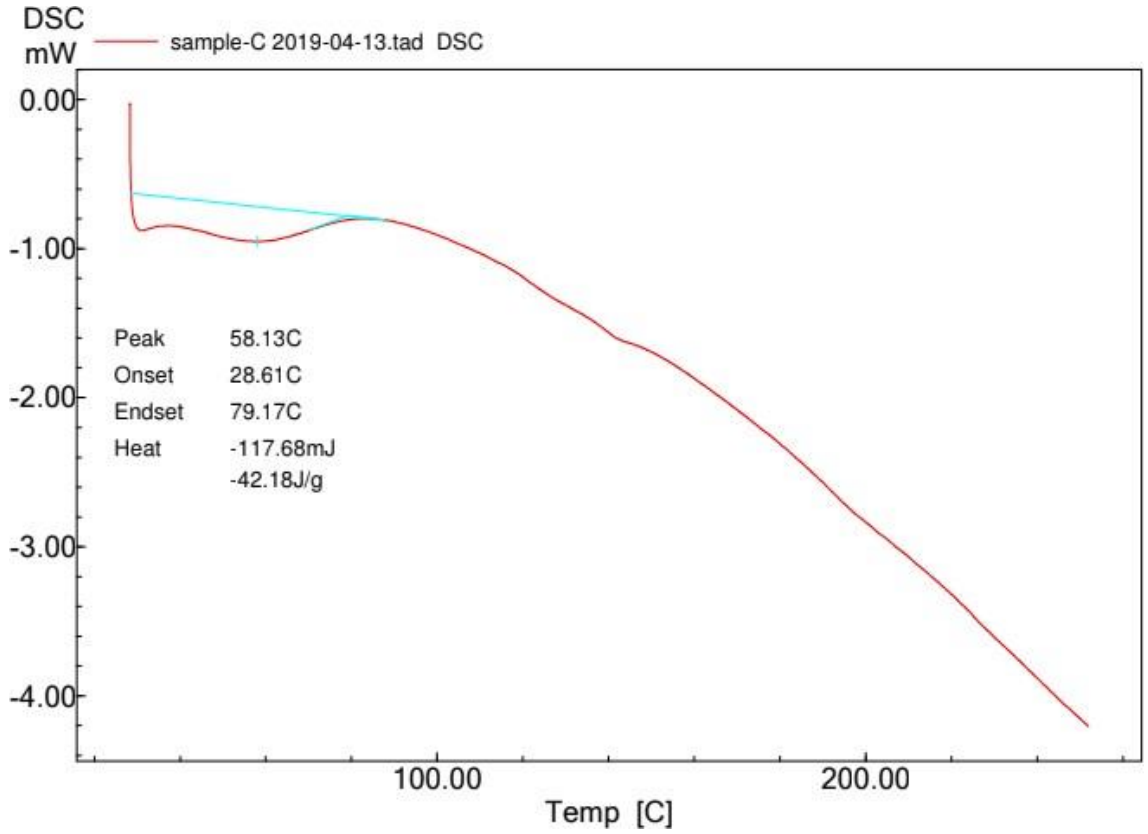


Figure No 9 DSC of Physical Mixture (Grinding Method)

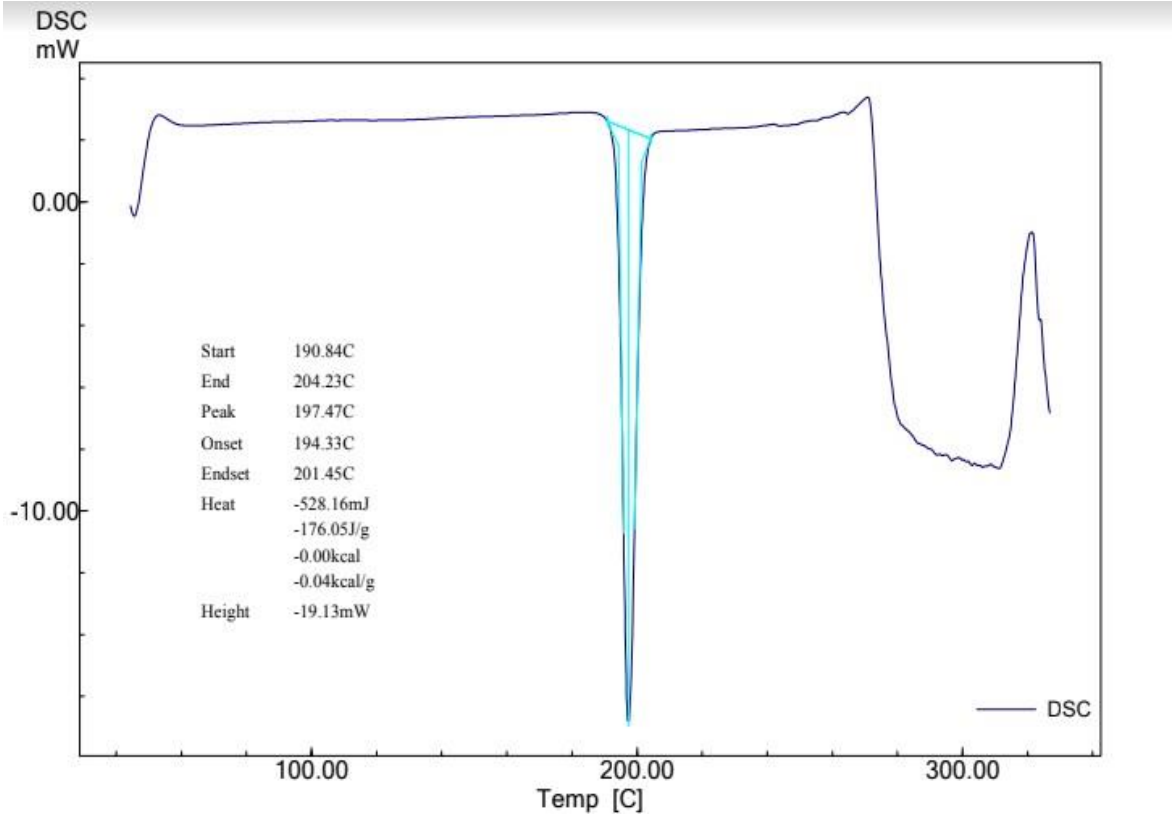


Figure No 10 DSC of physical mixture (Solvent Evaporation method)

The pure Prasugrel HCL shows a sharp endothermic peak at 186°C. The characteristic endothermic peak corresponding to melting peak of pure Prasugrel HCL was shifted towards higher temperature, in solid dispersion prepared by Solvent evaporation method. This could be attributed to Non-uniform distribution of Prasugrel Hydrochloride in the crust of polymer, resulting in poor miscibility of molten drug in polymer.

4.12. Drug Content:

1. Grinding method

Table No 12. Drug content of Grinding method.

Batch No	% Drug content
F2 (1:2)	65.16%

2. Solvent Evaporation Method

Table No 13. Drug content of Solvent evaporation Method

Batch No	% Drug content
S2 (1:2)	56.93%

4.13. Solubility Study:

1. Grinding method

Table No 14. Solubility of Grinding Method

Batch	F1(mg/ml)	F2(mg/ml)	F3(mg/ml)	F4(mg/ml)	API(mg/ml)
Water	0.6123	0.767	0.7283	0.6753	0.0020
pH 6.8	0.7477	0.8798	0.8304	0.7675	0.0024
0.1N HCL	0.9936	1.0013	0.8936	0.8763	0.0513

2. Solvent Evaporation Method

Table No 15. Solubility of Solvent Evaporation Method.

Batch	S1(mg/ml)	S2(mg/ml)	S3(mg/ml)	S4(mg/ml)	API(mg/ml)
Water	0.04518	0.04987	0.04753	0.4716	0.0020
pH 6.8	0.05267	0.06304	0.06280	0.05996	0.0024
0.1N HCL	0.4980	0.5817	0.5813	0.5447	0.0513

4.14. XRD Study

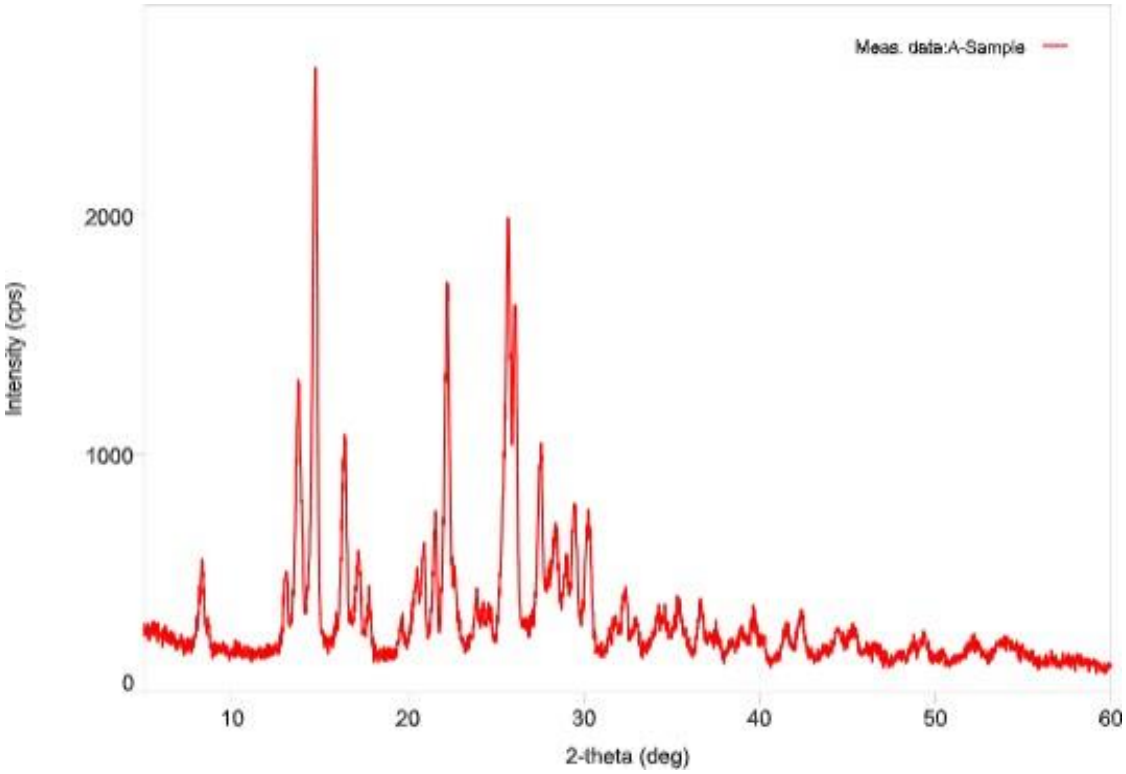


Figure No 11 XRD Spectra of Prasugrel HCL

.

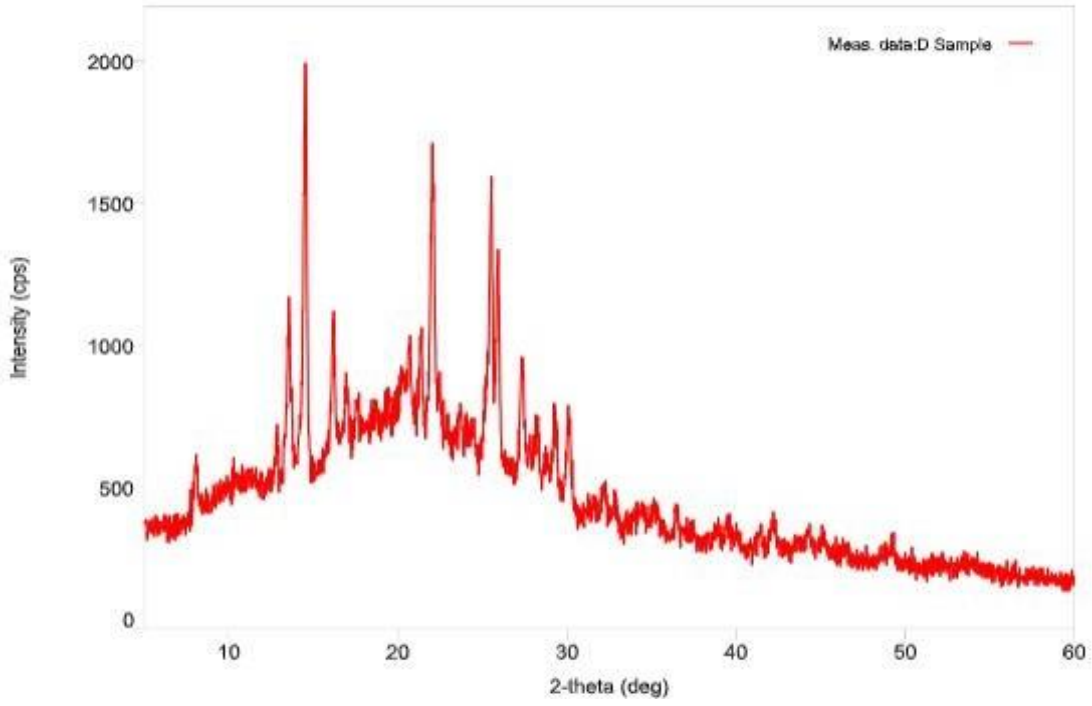


Figure No 12 XRD Spectra of Physical Mixture (Grinding Method)

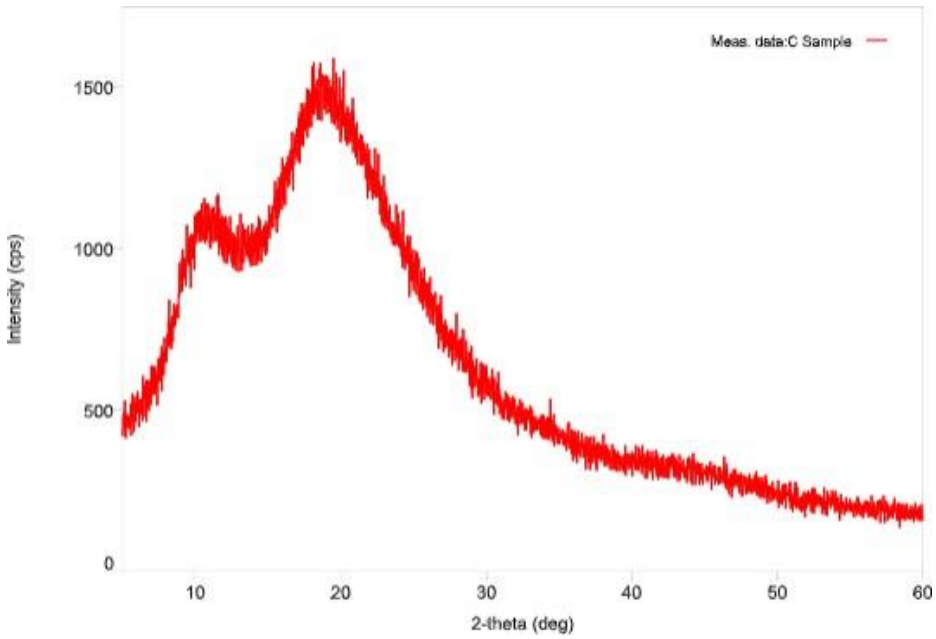


Fig No. 13 XRD Spectra of Physical Mixture (Solvent Evaporation Method)

XRD analysis is used to judge any changes in the crystallinity of the drug which precipitated in an amorphous form, when formulated into a solid dispersion. Powder XRD is used to study any changes in crystallinity of the drug which could be one of the mechanisms responsible for the improved dissolution. Powder XRD of pure Prasugrel HCL and solid dispersion by both Grinding method and solvent Evaporation Method are shown in Figure. The X-ray Diffractogram of pure Prasugrel HCL showed that the drug Prasugrel HCL was in crystalline in nature as shown in the XRD graph. The XRD of solid dispersion of Prasugrel HCL prepared with HPMC-AS by Grinding method showed that some peaks of the pure drug were absent and or intensity of the peaks was reduced. But the XRD of solid dispersion of Prasugrel HCL prepared with HPMC-AS by Solvent Evaporation method showed that still some peaks of the pure drug was present. Thus the result of Powder XRD indicates that the drug in solid dispersion in Grinding method is in amorphous form than the pure Prasugrel HCL. Results from solvent evaporation method reveal that drug still shows some crystalline nature. Thus the increased dissolution of the drug was observed more in Grinding method than the Solvent Evaporation Method.

4.15. Dissolution Study

Release of Prasugrel Hydrochloride from solid dispersion prepared by Grinding method found to be almost 90.9% within 30 min. and release from solid dispersion prepared with

solvent evaporation method found to be 84.1% within 30 min which is less as compared tosolid dispersion prepared with grinding method. In case of 1:3 ratio drug release was also increased but it was negligible than 1:2 ratio. So as per above observation it was concluded that 1:2 ratio is optimized ratio for the preparation of solid dispersion and above this ratio drug release was not found to be increasedmuch.

1. Grinding Method(% CDR)

Table No 15. Dissolution Study of Grinding Method

Time (min) →	0	5	10	15	20	25	30
API % release	0	18.54	20.97	26.76	31.5	35.18	42.22
F1 % release	0	44.1	50.15	59.59	65.79	74.28	85.08
F2 % release	0	48.55	53.53	64.12	70.38	81.14	90.9
F3 % release	0	41.87	45.68	56.18	65.68	71.95	79.39
F4 % release	0	38.54	43.42	48.35	54.42	58.35	70.08

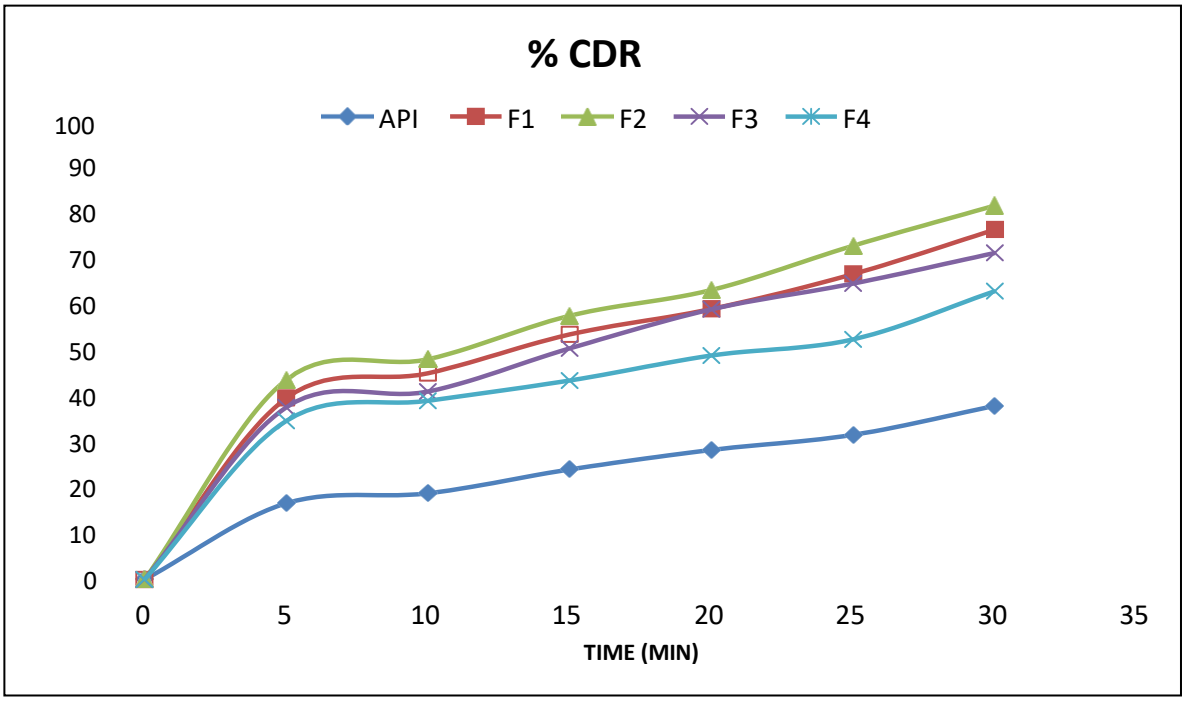


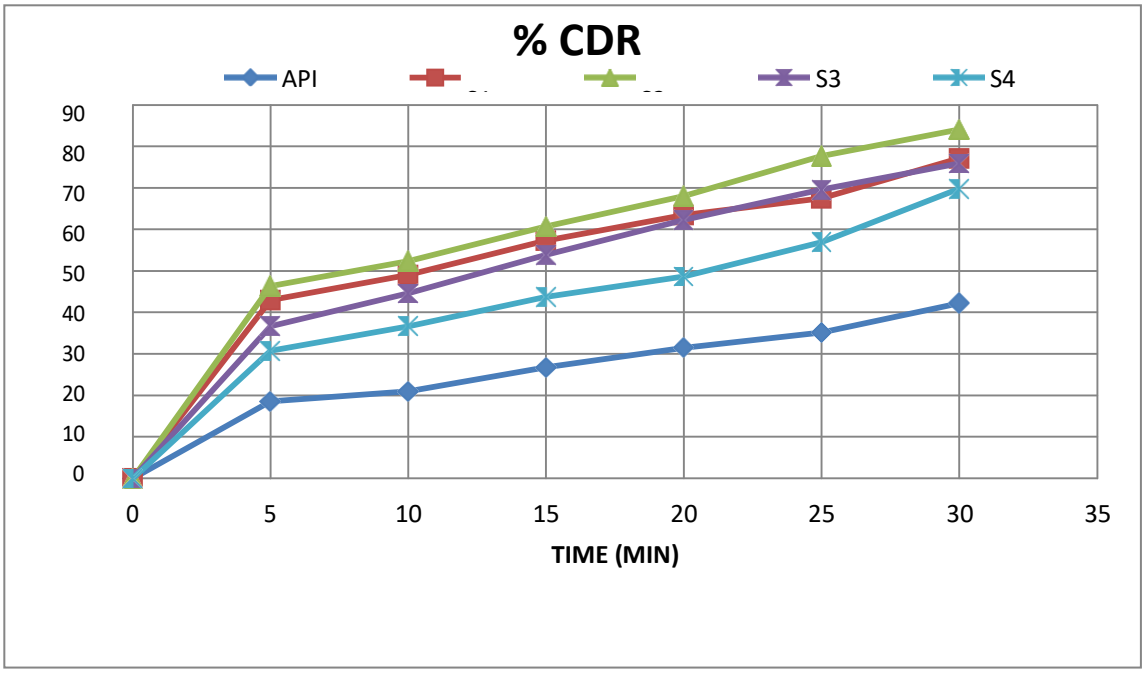
Figure No 14 Dissolution profile of pure drug and solid dispersion in phosphate Buffer 6.8 (Grinding method).

2. Solvent Evaporation Method (%CDR)

Table No 16. Dissolution Study of solvent evaporation Method

Time (min) →	0	5	10	15	20	25	30
API % release	0	18.54	20.97	26.76	31.5	35.18	42.22
S1 % release	0	42.99	49.03	57.34	63.52	67.54	77.16
S2 % release	0	46.33	52.4	60.75	68.08	77.71	84.1
S3 % release	0	36.66	44.57	53.88	62.26	69.59	56.96
S4 % release	0	30.77	36.67	43.73	48.66	56.96	69.8

Figure No 15 Dissolution profile of pure drug and solid dispersion in phosphate Buffer 6.8 (Solvent evaporation method).



1. Comparison of Dissolution Profile between Grinding method and Solvent Evaporation Method.

Table No 17. Comparison of Dissolution Study between two methods.

Time (min)	0	5	10	15	20	25	30
F2 % Release	0	48.55	53.53	64.12	70.38	81.14	90.9
S2 % Release	0	46.33	52.4	60.75	68.08	77.71	84.1

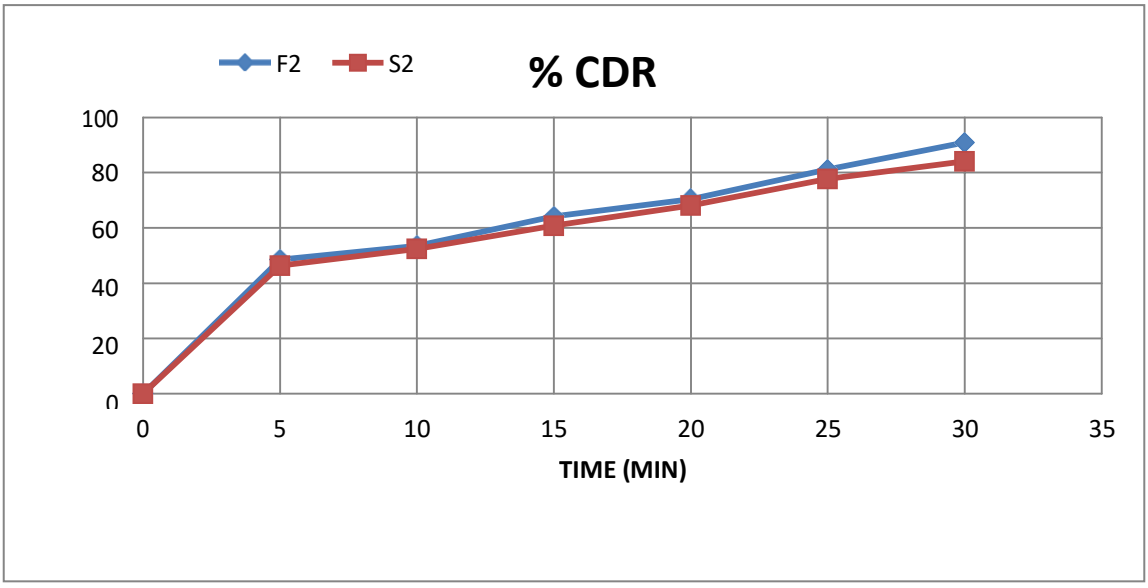


Figure No 16 Comparison of Dissolution profile between optimized batches ofSolid dispersion prepared by Grinding method and solvent evaporation Method in phosphate buffer 6.8.

5. CONCLUSION:

From Preformulation study it was concluded that Drug and Polymer were found to be as per standards.

From IR and DSC studies it can be revealed that Drug and Polymer were compatible.

Solid dispersion was prepared by two preferable methods (Grinding method, Solvent evaporation method) by using different drug polymer ratio (1:1, 1:2, 1:3, 1:4). In solid dispersion solubility was

increased with increased concentration of HPMC-AS. Solid dispersion prepared by using 1:2 drug:polymer ratio show significant increase in solubility than the other drug polymer ratio from both the methods. From XRD Analysis it can be concluded that drug in solid dispersion prepared by Grinding method is in amorphous form than the pure Prasugrel HCL. Thus the higher dissolution of the drug was observed from solid dispersion prepared by Grinding method.

In case of solid dispersion prepared by solvent evaporation method drug is in amorphous form but still shows some crystalline nature, hence dissolution is lesser from solvent evaporation method as compared to grinding method. From comparison of dissolution profile between two methods it was found that drug release was increased only upto 1:2 ratio. In case of solid dispersion prepared by grinding method F2(1:2) was the optimized batch and % CDR showed 94.4% at the end of 30 min. similarly in case of solid dispersion prepared by solvent evaporation method S2(1:2) was the optimized batch and % CDR showed 84.1 at the end of 30 min which is less as compared with the % CDR of solid dispersion prepared by Grinding method.

Finally, it is concluded that solid dispersion method and HPMC-AS as a carrier for solid dispersion preparation are useful for dissolution rate improvement of poorly soluble drug like Prasugrel HCL in aqueous media as well as at high pH conditions.

6. REFERENCES

1. MegaJ. L., SimonT. Pharmacology of antithrombotic drugs: An assessment of oral antiplatelet and anticoagulant treatments.The Lancet.2015; 1–10.
2. Eli Lilly Nederland B. V. DOC. Ref: EMEA/117561/2009.
3. QuatromoniN. *et al.* Novel Anti-platelet Agents in Acute Coronary Syndrome: Mechanisms of Action and Opportunities to Tailor Therapy.CurrentAtherosclerosis Reports,2015; 1–10.
4. GukathasanN.,Mehran R.Acute Coronary Syndromes: Advances in Antithrombotics', Current Atherosclerosis Reports.2013; 1–8.
5. Bramhankar D.M., S. B. J.Biopharmaceutics and Pharmacokinetics.VallabhPrakashan.2009;27-35.
6. Nikghalb L. A.*et al.*Solid Dispersion: Methods and Polymers to increase the solubility of poorly Soluble Drugs. Journal of Applied Pharmaceutical Science. 2012;2(10):170–175.
7. Devara R.K,Reddipogu P.,Kumar S. ,Rambabu B., Jithan A., H. M. Investigation of Solubility Enhancement of Prasugrel Hydrochloride: Nanosuspensions and Cyclodextrin Inclusion Complexes.Indian Drugs. 2014;51(02): 29–38.
8. Junda Cen, Jiangsu (CN); Chun-hong Zhang, Jiangsu (CN); Qi Zhang, Jiangsu (CN);

Aifeng Li, J. (CN).Pharmaceutical composition for improving dissolution rate of prasugrel and its preparation method.2015;*US Patent, US 9,050,328B2*.

9. Zecevic D*et al.* Site-specific solubility improvement using solid dispersions of HPMC-AS/HPC SSL – Mixtures. European Journal of Pharmaceutics and Biopharmaceutics. 2014;87(2): 1–7.
10. Ghareeb M*et al.* Kneading Technique for Preparation of Binary Solid Dispersion of Meloxicam with Poloxamer 188.AAPS Pharm Sci Tech. 2009;10(4): 1206–1215.
11. Tanno F.*et al.*Evaluation of Hypromellose Acetate Succinate (HPMCAS) as a Carrier in Solid Dispersions.Drug Development and Industrial Pharmacy. 2004;30(1): 9–17.
12. Maulvi F. A.*et al.* Improvement of Dissolution Rate of Aceclofenac by Solid Dispersion Technique, Powder Technology. 2011;207: 47–54.
13. Thirupathaia A., Sunder R. S. Enhancement of Solubility and Dissolution of Atorvastatin by Solid Dispersion Technique with Novel Carriers', Scholars Research Library. 2016;8(8): 180–191.
14. Choudhary D., Kumar S., Enhancement of solubility and dissolution of glipizide by solid dispersion(kneading) technique. Asian Journal of Pharmaceutics.2019;245–251.
15. NikghalbL. A. *et al.* Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble Drugs. Journal of Applied Pharmaceutical Science. 2012;2(10): 170–175.
16. Schrör K., Siller-Matula,Huber, K. Pharmacokinetic basis of the antiplatelet action of Prasugrel. Fundamental and Clinical Pharmacology. 2012;26: 39–46.
17. Ashland. Physical and Chemical Properties Handbook (Aquasolve-Hydroxy propylmethylcellulose acetate succinate.2016;1-15.
18. The Indian Pharmacopoeia. Government of India ministry of Health and Family Welfare. Published byThe Indian Pharmacopoeia commission Ghaziabad, 2007;2: 480.
19. Donald L. Pavia, Gary M. Lampman, G. S. K.Introduction to Spectroscopy.2001;1328.
20. Kanwar N., KumarR. Sinha, V. R. Preparation and Evaluation of Multi-Particulate System (Pellets) of Prasugrel Hydrochloride. Open Pharmaceutical Sciences Journal. 2015; 2: 74–80.
21. Shrestha P., BhandariS. K., Adhikari, S.Design and Development of Immediate and Sustained Release Tablets. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2014; 5(811): 1056–1064.
22. Rumondor, A. C. F., Dhareshwar, S. S. Kesisoglou, F. Amorphous Solid Dispersions or Prodrugs: Complementary Strategies to Increase Drug Absorption. Journal of Pharmaceutical Sciences. 2016;105: 1–11.

23. Chandira R.M., Palanisamy P.,Jaykar B., Pasupathi1 A., Sreedharan D. B. Formulation, Development and Evaluation of Immediate Release Tablets of Prasugrel. world Journal of Pharmaceutical Research. 2015;4(8): 1421–1437.
24. Kim K.S.*et al.* Development of novel Prasugrel base Microsphere-loaded Tablet with enhanced stability: Physicochemical characterization and in vivo Evaluation in Beagle Dogs. Colloids and Surfaces B: Biointerfaces. 2016;146: 754–761.
25. Balogh A., Farkas B., Palv€olgyi A., Domokos A., Demuth B., MarosiG., Z. K. N.Novel Alternating Current Electrospinning of Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS) Nano fibers for Dissolution Enhancement: The Importance of Solution Conductivity. Journal of Pharmaceutical Sciences. 2017;106: 1634–1643.
26. Al-Obaidi H. Buckton, Evaluation of Griseofulvin Binary and Ternary Solid Dispersions with HPMCAS.AAPS Pharm SciTech. 2009;10(4): 1172–1177.
27. Curatolo W., NightingaleJ. A., Herbig, S. M. Utility of hydroxypropylmethylcellulose Acetate Succinate (HPMCAS) for Initiation and Maintenance of Drug Supersaturation in the GI Milieu. Pharmaceutical Research. 2009;26(6): 1419–1431.
28. Friesen D. T. *et al.* Hydroxypropyl Methylcellulose Acetate Succinate-Based Spray-Dried Dispersions: An Overview Dwayne. Molecular Pharmaceutics. 2008;5(6): 1003–1019.
29. ChiouW. L., Riegelman S. Pharmaceutical Applications of Solid DispersionSystems. Journal of Pharmaceutical Sciences. 1971;60(9): 1281–1302.
30. BakerW. L., WhiteC. M.Role of prasugrel, a novel P2Y12 receptor antagonist, in the Management of Acute Coronary Syndromes', American Journal of Cardiovascular Drugs. 2009; 9(4): 213–229.