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International Journal of Advances in Pharmaceutics 2 (2) 2013

International Journal of Advances in Pharmaceutics

Journal home page:http://ijap.ssjournals.com

Research Article

Evaluation of anti-moisture effect of HPMC, Kollidon CL and Aerosil - 200 in hydrolysis affinity Clopidogrel-Aspirin tablet using Delta T Moister Sensor

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Keywords:

Aspirin,
Clopidogrel,
Moisture,
Water activity,
Delta T model,
Kollidon CL,
Aerosil 200,
HPMC 15 cps,
Dissolution

Abstract

The combined therapeutic effect of aspirin and clopidogrel is more potent than single one. This combined formulation is not stable due to their moisture affinity toward the hydrolysis reaction. The presence of moisture is a crucial factor in any formulation and causes sticking, picking, microbial growth, stability issues, lamination, friability. This combination formulation was designed using hydroxypropylmethyl cellulose 15 cps, Kollidon CL and Aerosil 200 in a controlled clean room class-I to stop the hydrolysis reaction. The tablets were made using slug method and hardness, disintegration, friability, dissolution, drug content, water activity, moisture content was determined. Kollidon CL and Aerosil 200 showed greater moisture reduction rate than HPMC 15 cps. The better anti-moisture effect of the excipient of Kollidon CL and Aerosil 200 was assured by the calculation of water activity using delta T sensor and isotherm, hysteresis. The quantity of excipients in the tablets was demonstrated for the significant affinity to moisture. The investigated simulated amount of Kollidon CL and Aerosil 200 showed the effective lower water activity in the delta T sensor. The mean moisture specification range was considered as 0.5-4.0% while the kollidon CL and Aerosol 200 showed moisture content of 1.32% and water activity (aw)of 0.014. In this study the Delta T sensor is used due to its significant reduction of dead time from 30% to 45% and moisture variation reduced at least 30% than other models treatment.

1. Introduction

Aspirin (2-acetyloxy benzoic acid) is one type of cyclooxygenase inhibitor and Clopidogrel bisulphate (methyl (s)-2-chlorophenyl (4,5,6,7- tetrahydothioeno-[3,2-C]pyridine-5-yl) acetate bisulphate) which is an ADP antagonist, are two major anti-thrombogenic agents[1,2,3]. Aspirin is effective to prevent the primary and secondary myocardial infarction, cardiovascular death and stroke[4,5,6] and Clopidogrel is a second generation thienopyridine with a better tolerability profile than first generation thienopyridines (ticlopidine).The combined dosage formulation of Aspirin and Clopidogrel Bisulphate is useful as antiplatelet agents. The combination of Clopidogrel and Aspirin is demonstrated for the treatment of acute coronary syndromes especially in Unstable Angina, and Percutaneous Coronary Interventions[6,7,8]. This combined formulation provides a greater inhibition of platelet activity than Aspirin alone in patients after recent ischemic stroke[9]. This combined antiplatelet therapy has an important role for patients with established cardiovascular disease. Combined use of these two drugs produces enhanced therapeutic effect. Aspirin and Clopidogrel both are esters and have a tendency to hydrolysis which reduces therapeutic activity[10]. Both the drugs are susceptible to neutral and oxidative-degradation, dry heat

degradation, photo-degradation to different extent in different stress conditions[11]. Cellulose is generally moisture affinity excipients to change the solid properties in the tablet[12,13]. The influence of moisture on the physical state of the tablet, and the effect of sorbed moisture on the chemical stability of moisture sensitive drugs is most important, particularly because Asprin are expensive moisture-sensitive active ingredients.

Hageman[14] reported the effect of water content and activity on the solid-state stability to change in dynamic activity, conformational stability, participation of water as a reactant or inhibitor, and as a medium for mobilization of reactants.

Leesonet al[15] assumed that a layer of moisture sufficiently mobile to permit dissolution of the drug substance surrounded the solid particle. The remained saturated layer with drug caused zero order degradation process:

$$-dM/dt = K_s[H_2O]$$

where, –dM/dt is the rate of drug loss, k is a rate constant appropriate for the order of the reaction, S is the saturation concentration of the drug in the layer, and (H_2O) is the concentration of water.

Moisture is always present in a tablet even in a mixture of a small quantity of a minimum number of excipients in a dry blend with a small quantity of a single active. Too much moisture causes sticking, picking, microbial growth, stability issues while too little causes lamination. Tablets are friable due to low moisture content, insufficient binder, tablet configuration (e.g. sharp versus beveled edges). High content of moisture in tablet may cause to low assay content, product degradation, hardness reduction, dissolution differences. So it is required to keep appropriate moisture in the tablets. The mean moisture specification range is of 0.5-4.0% as a guideline for consideration, the smaller the tablet, the lower the quantity of moisture necessary for a successful tablet. But this rule of thumb has many exceptions[16]. Even moisture affected the matrix tablets after coating by the amorphous polymer[17].Water in tablets exists in four typical forms dissolved including when water concentration in tablet is below its saturation level, chemically bound water, free water, water adsorbed in excipients.

Therefore, in this study the anti-moisture effect of HPMC, Kollidon CL and Aerosil 200 in moisture sensitive Aspirin-Clopidogrel tablet was investigated using the delta T model.

2. Experimental

2.1 Materials: Aspirin, Clopidogrel Bisulpahte were obtained from Shanghai Shenging Phr. Factory with the potency of 100.10%. HPMC bought from Dow Chemical, USA and Kollidon CL, Magnesium Stearate, Flowlac and Aerosil200 were collected from Whichers & helm Gmbh & Co.

2.2 Method

2.2.1 Preparation of Tablets: Aspirin and Clopidogrel tablets were prepared using slug method. The tablets were prepared by slug method in seven steps. In the first step 98 mg of Clopidogrel and 5 mg of magnesium stearate were added in blender after sieving for 5 minutes. 80 mg of Aspirin was added to the blend and mixed again for 5 minutes in the second step. Then in the third step as diluents, 80 mg of Flowlac were sieved and mixed for 10 minutes with HPMC, Kollidon CL and Aerosil as Table I. At later in the fourth step, the blend was slugged and crushed through 19 meshes. After then the 4th step mixture was blended with 20 mg of Flowlac. At next in the sixth step the blend was analyzed to test the blend uniformity and finally the tablets were compressed using 10 mm die and flat faced punch (KBR Press, India and Die, USA). Sufficient compression load was applied in order to produce tablets with the hardness of 50N to 100 N.

Table I: Formulation of Aspirin –Clopidogrel tablet

Formulation	Kollidon CL(mg)	Aerosil 200(mg)	HPMC(mg)	Moisture%
F1	10	5	-	1.32
F2	5	-	18	2.84
F3	-	5	-	1.68
F4	10	10	18	2.14
F5	5	5	18	2.68
F6	5	5	-	1.68

2.2.2 Physical Testing of the Tablet: Thickness and diameter of the tablets were measured by digital vernier calipers. The crushing strength of the tablets determined at room temperature by diametric compression using a hardness tester (Veego Scientific devices, India). The percentage friability of the tablets was determined using the tablet friability apparatus (Veego Scientific devices, India) operated at 25 rpm for 4 minutes. Tablets were weighed accurately placed in the chamber and rotated for 4 minutes (100 rotations). At the end of the run, the dusts on the tablet cleaned carefully, weighed accurately again and the percent friability (f) computed from the weight of the tablets before and after the test according to the below equation:

$$f = \left(1 - \frac{W}{Wo}\right) \times 100$$

where, Wo and W are the weights of tablets before and after the test respectively.

2.2.3 Flow properties: The bulk density of the powder was determined by weight of the powder divided by the volume it occupies, normally expressed as g/ml. Tap density was determined by subjecting the powder in a graduated cylinder to 500 taps by a standardized tapping procedure of USP –II method (using VTAP MATIC-II) by following equation:

$$\text{Tapped density} = \frac{Mass\ of\ powder}{tapped\ volume}$$

The hausner's ratio was determined as the ratio of the initial bulk volume to the tapped volume. The carr's index was calculated using bulk and tapped densities data by following equation:

$$\text{Carr's index} = \frac{tapped\ density - bulk\ density}{tapped\ density} \times 100\%$$

2.2.4 Simultaneous determination of Aspirin and Clopidogrel: For combined formulation of Aspirin and Clopidogrel C18 column, 237 nm of wavelength, 15 ml/min of flow rate, mobile phase as diluents and water: CAN: Phosphoric acid (600:400:2 ml) as mobile phase were used in HPLC analysis.

***2.2.5 In-vitro* Dissolution studies:** The dissolution study was done in two ways one is Dissolution profile study and another is Dissolution Q point study.

2.2.6 Dissolution profile study: The in-vitro drug release studies of Aspirin and Clopidogrel tablets were determined using USP dissolution apparatus I (DT-6, ZT 322, ERWEKA, Germany). The dissolution testing was performed using 900 ml 0.1 N HCL at 50 rpm and 37 0.5˚C temperature for 45 minutes.

2.2.7 Dissolution "Q" point study: The parameters of dissolution apparatus were set, added one tablet into each of six dissolution vessels. The dissolution apparatus was immediately started. 10mL of the sample solution was withdrawn at the end of 45 minutes from each dissolution vessel. This solution was filtered through 0.45µ membrane filter, filled into vials and labeled appropriately.

2.2.8 Moisture content and water activity determination

The moisture content was determined by Karl-Fisher apparatus and in the method 30ml of dried methanol was taken in KF apparatus beaker, and neutralized with fresh KF reagent. Accurately weighed quantity of powdered tablet was transferred into the neutralized methanol present in the

beaker. The titer value was noted.

Laboratory test setup was used as figure 1 to obtain the moisture content. A 100 ml Erlenmeyer glass flask was setup to prevent the ambient moisture ingress during KF sampling. Magnetic stirrer and heater with external temperature regulation probe were used to find the constant temperature. Delta T moisture sensor (ML2x Theta Probe, Delta-T devices, UK.) was inserted into the flask and connected to the personal computer through a digital rs-232 output to read the moisture content. The test instruments were accurate according to the manufacturer calibration specification report (temperature accuracy error <0, 5 C, including non-linearity, hysteresis and repeatability errors).

Figure 1: A link test setup, left: moisture sensor (Delta T) and Metrohm 756 karl fischer Coulometer.

2.2.9 Moisture Content Prediction: Moisture content was predicted from the isotherm. The isotherm was characterized by Delta T model and then loading that model into a specialized water activity instrument of Decagon's AquaLab Series 4TE DUO.

2.3 Statistical Analysis: Data were analyzed with the logistic regression techniques of SAS (Version 6.12). The dependent variable was the tablets. The independent variables were aw and MC of the tablets.

3. Results

The weight, diameter, and thickness was in the range of 288.2 ± 1.5793 to 321.8 ± 1.6603, 10.104 ± 1.6101 to 10.146 ± 1.3886 and 2.98 ± 1.5801 to 4.87± 1.6661 respectively but hardness of tablets were increased with the amount of pressure. The percent friability was less than 0.5%. The data obtained showed in the following table II:

Table II: Physical characteristics of Aspirin - Clopidogrel tablet

Formulation	Avg. Wt. (mg.)	Avg. Diameter (mm.)	Avg. Thickness (mm.)	Hardness (N)	Friability (in percent)
F-1	298.8± 0.0647	10.146± 1.3886	3.5±20.0716	53	0.06
F-2	306.6± 1.3876	10.111± 1.5801	2.9±80.0716	99.85	0.00
F-3	288.2± 1.5793	10.122± 1.6620	3.9±81.3886	58	0.35
F-4	321.8± 1.6603	10.122± 1.6531	2.9±81.5801	99.85	0.00
F-5	311.2± 1.6688	10.122± 1.6602	4.0±91.6621	101.2	0.00
F-6	293.6± 1.6180	10.104± 1.6101	4.8±71.6661	66	0.50

The percentage content of Aspirin and Clopidogrel was minimum 77.99% and 76.98% respectively. The disintegration time was found less than 4% as shown in Table III.

Table III: Drug content and disintegration time of Aspirin and Clopidogrel tablet at the first month

Formulation	Drug Content (mg) Aspirin & Clopidogrel	Disintegration (min)
F1	78.91, 98.98	3.33
F2	78.95, 98.19	3.03
F3	78.42, 98.99	3.18
F4	78.55, 98.92	3.20
F5	77.99, 98.01	4.25
F6	78.05, 98.25	2.35

The bulk density of the granules was between 0.788 g/cm^3 to 0.322 g/cm^3 indicating good packing capacity of granules. Tapped density of the granules was between 0.866 g/cm^3 to 0.375 g/cm^3 showing good flow characteristics. Carr's index, Hausner's ratio and angle of repose of the granules were within the range indicating good flowability and results showed in the table IV:

Table IV: Flow properties of granules

Formulation	Compressibility Index (in percent)	Hausner Ratio	Angle of Repose (Degree)
F-1	20.000	1.250	39.8
F-2	22.223	1.286	39.8
F-3	50.000	2.000	39.8
F-4	28.578	1.400	37.56
F-5	20.000	1.250	37.56
F-6	16.667	1.200	35.53

Figure 2-7 showed the moisture control and water activity of dry tablets in isotherm graph. F1 tablets showed effective water activity and moisture content of 0.014 to 0.079 and 1.32% to 1.96% respectively. The aw and MC of F3 and F6 was close to F1 tablets. The F2, F3, F4, F5, F6 showed the aw of 0.387, 0.193, 0.717, 0.239, 0.205 and MC of 4.14%, 2.78%, 3.99%, 3.98%, 2.89% respectively. Notice that there was no tablet found above the critical aw value when using the Delta T.

Fig 2. Sorption isotherms of F1 tablets

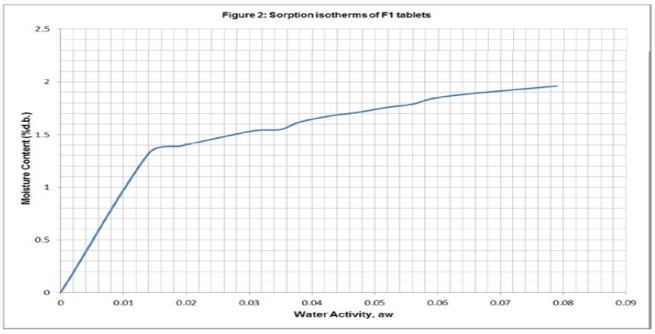


Fig 3. Sorption isotherms of F2 tablets

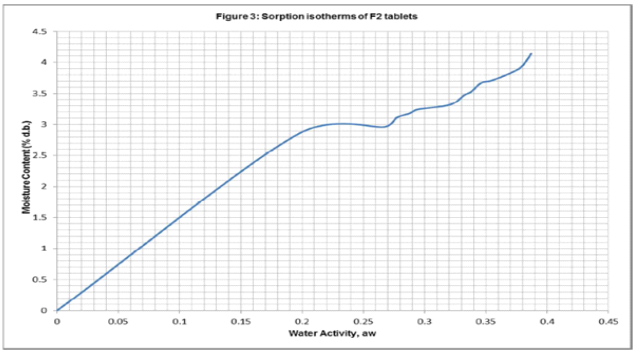


Fig. 4. Sorption isotherms of F3 tablets

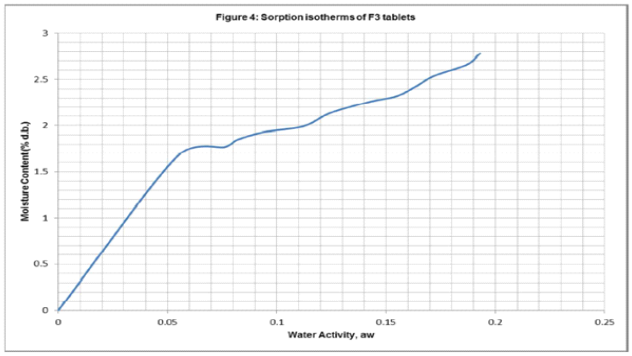


Fig. 5 Sorption isotherms of F4 tablets

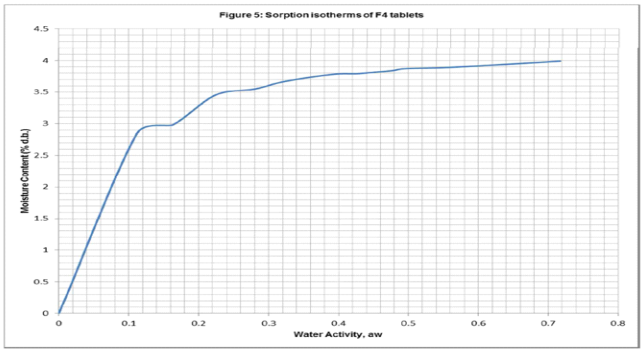


Fig. 6 Sorption isotherms of F5 tablets

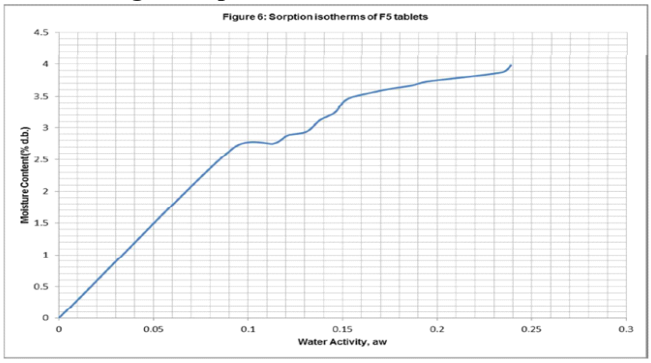
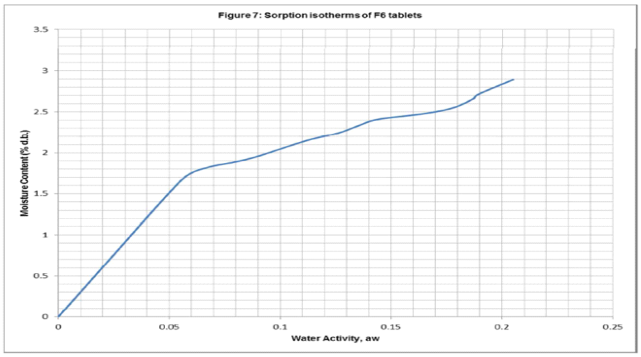


Fig 7 Sorption isotherms of F6 tablets



After three months, the maximum dissolution rate of aspirin was found 95.79% in F5 tablets and minimum of 60.68% in F1 tablets at the 30 C, 60% RH but 92.98% and 42.29% was found in F3 and F2 tablets at 40 C, 75% RH. The range of dissolution rate was 113.33% to 98.83% at 30 C, 60% RH and 113.12% to 83.81% at 40 C, 75% RH found for Clopidogrel in F5, F1, F5, F2 respectively. These results were shown in figure 8 and 9.

Fig 8 Percent Dissolution of Aspirin-Clopidogrel immediate release tablets at 30°C, 60% RH and 40°C, 75% RH

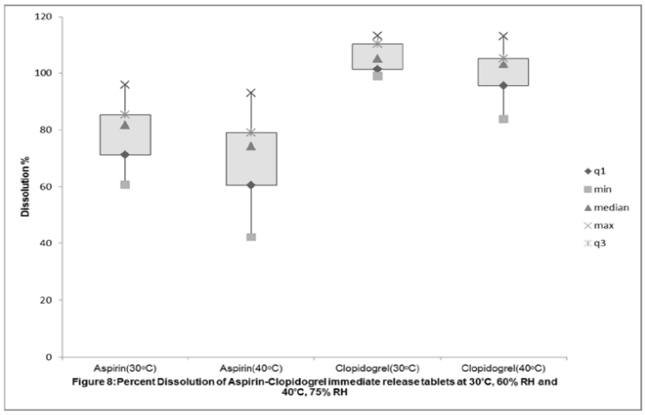


Figure 8:Percent Dissolution of Aspirin-Clopidogrel immediate release tablets at 30°C, 60% RH and 40°C, 75% RH

Fig 9. Drug content of Aspirin-Clopidogrel immediate release tablets at 30°C, 60% RH and 40°C, 75% RH

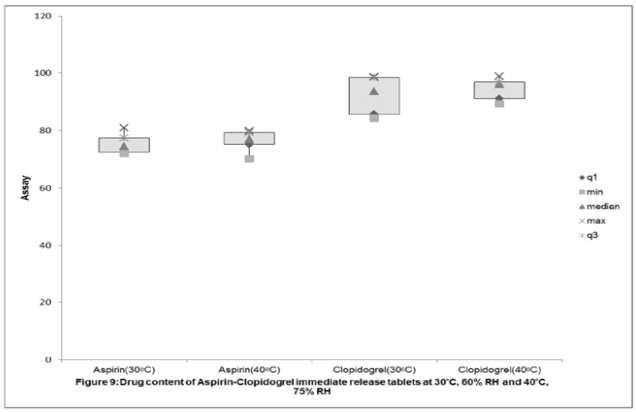


Figure 9:Drug content of Aspirin-Clopidogrel immediate release tablets at 30°C, 60% RH and 40°C, 75% RH

4. Discussion

The Aspirin-Clopidogrel combination formulation was not stable due to sensitivity of Aspirin to moisture and Aspirin was gradually hydrolyzed in contact with moisture to acetic acid and salisylic acid. The selection of excipients and storage condition played an important role to develop a stable formulation. After developing this combined formulation with many types of excipients, it was found that very simple formulation made possible than conventional formulations using Kollidon CL, Aerosil-200 and HPMC 15 cps. The quantity of these excipients was maintained in a simulated way and adjusted to effective quantity for the more moisture controlled formulation. The hardness, thickness, diameter, friability, Hausner's ratio, carr'x index, angle of repose, disintegration were determined and found very little resemblance to moisture results. The HPMC 15 cps contained formulation showed no friability of 0.00% than Kollidon CL and Aerosil-200of 0.06% to 0.50%.The flow properties parameters of Hausner's ratio, angle of repose and Carr's index also were better for F1 to F6 tablets. After preparation of tablets, drug content of F1 to F6 tablets was 77.99% to 78.95% of Aspirin and 98.01% to 98.99% of Clopidogrel was found.

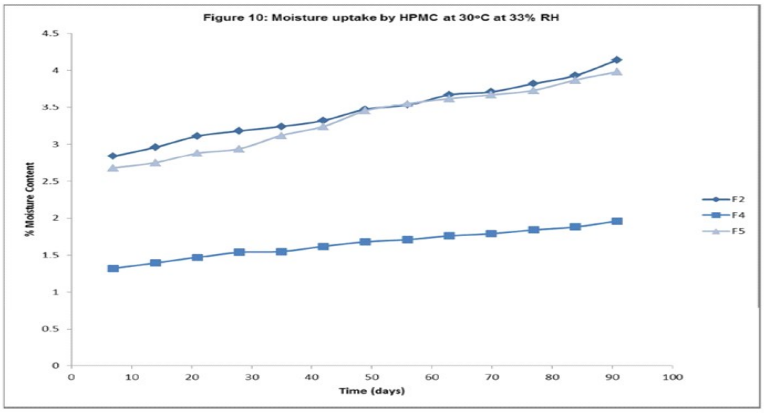
After three months, the moisture content and water activity was determined for the stability test of the tablets. The MC (moisture content) and water activity affected the tablets drug content, dissolution and stability of formulation. The conventional method did not prevent the moisture variations so that delta T moisture sensor was utilized with KF to remove these variations (figure 2-7) and found optimum moisture content and water activity. More importantly, the excipients quantity and variations affect the moisture content and water activity. It was found that the unequal amount of Kollidon CL and Aerosil-200 with 10 mg and 5 mg respectively prevented the moisture as well as hydrolysis reaction. But the HPMC 15 cps contained F2, F4 and F5 tablets showed more moisture content of 2.84%, 2.14%, 2.68% respectively and water activity than HPMC free formulations. The fact behind this may be for the formation of salicylic acid to expose the moisture adsorption sites of higher energy on aspirin[17], thereby leading to the acquisition of more water and effect on the performance of excipients.

The moisture sorption isotherm[13] was showed in figure 2 to 7 because it is widely used to determine the affinity of substance to water and the water content showed the lower rate of storability, agglomeration of powders, microbiological stability, flow properties, viscosity, dry substance content, concentration or purity, and nutritional value of the product.

Crystal formation was found on the tablets of F2, F4, F5for the presence of moisture that was also noted in the published study[18]. HPMC prepared tablet of F2, F4, F5 using slug method showed increased moisture content considerably with the time (figure 10) whereas the study of Carstensen *et al*[23] found this increased rate in the first few days of preparation[18]. It was found that surface of the tablets converted to the crystalline form and the change of physical structure to dense amorphous structure due to the absorption of moisture by the HPMC and a proportionate induction in moisture

content. The reason may be for lower glass transition temperature due to absorption of water into the bulk structure of the solid and plasticizer activity of water[19]. Another reason may be the presence of HPMC in the formulation influenced product stability due to concept of moisture scavenger in the formulation.

Fig. 10 Moisture uptake by HPMC at 30°C at 33% RH



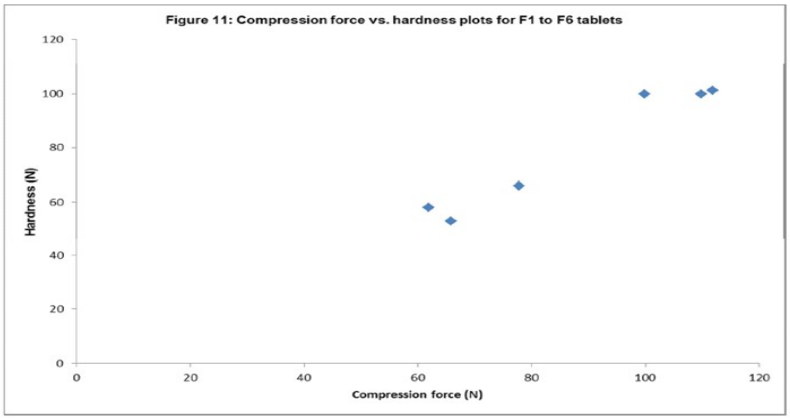
The tablets of F2, F4, F5 showed a higher moisture content and water activity than F1, F3, F6 but this parameters were under controlled due to our formulation design. This method was so simple and convenient than other published study of using correction of monolayer capacities of microcrystalline cellulose for degree of crystallinity[20].

The tablets of F1 to F6 showed very lower acceptable MC although adsorbent was not used in the prepared formulations (F1 to F6).

The profiles of hardness versus compression of tablets showed a line (figure 11) whose slope appeared to be functions of moisture content. But compressibility index with adsorbed moisture did not show a linear function.

The studied results of Aspirin tablet showed no degradation due to very little amount of increased moisture content and water activity than other published study whereas after 120 days the degradation of aspirin powder was found more than ten times greater than what would be expected based on suspension data at 100% RH and 250C. The rate of aspirin degradation was found to increase with time[21].

Fig 11. Compression force vs. hardness plots for F1 to F6 tablets



No complication was faced during preparation of moisture sensitive drug of aspirin in combination with Clopidogrel with hydrophilic excipient (HPMC) unlike other authors[22]. HPMC contained formulations of the F2, F4, F5 tablets had below the 11%moisture content and the water activity (aw) above the specification of 0.15.

The disintegrant was not used in the present study. The reason for this was the water associated with the system may tightly bound to the disintegrants. The degradation of the tablets and hydrolysis reaction may be for the intermediate humidity of the excipient. This affected the sorption process and acid catalysis[22]. Thus in the present study it was tried to make tablet without disintegrates with optimum disintegration.

5. Conclusion

Finally, it was concluded that moisture affects the pharmaceutical formulation at any condition. This may happen gradually or initially. Many studies have been attempted to overcome this problem for the stable combination formulation for Aspirin and Clopidogrel. But Aspirin is moisture sensitive and hence unstable. It degrades due to hydrolysis reaction in presence of moisture. This tendency was controlled using optimum amount of excipients of Kollidon CL and Aerosil 200. HPMC also is moisture sensitive excipients. But our experimental design controlled this moisture tendency of Aspirin and HPMC using the Delta T moisture sensor. So, it is taken together said that optimum quantity of Kollidon CL, Aerosil 200 with the setup of Delta T moisture sensor is a promising technology. It is suggested to apply the delta T moisture sensor for pharmaceutical interest because the conventional moisture determination method is not suitable due to variation in results and effective control of moisture content and water activity.

References

1. Satoskar R S, B.S.D., Ainepure S S, Pharmacology and Pharmacotherapeutics. 3rd edition ed., Mumbai: *Mumbai Prakashan*, 1997, p 462.
2. D, T.K., Essentials of Medical Pharmacology. 5th ed., New Delhi: *Jaypee Brothers Medical publishers (P) ltd.* 2004, p 560.
3. O' Neil M J, S.A., The Merck Index. 13th edition ed., New Jersey: *Merck and Co., INC.* Whitehouse station, 2001, p 856 & 2421.
4. BMJ, Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration, *British Medical Journal*, 1994. 308(6921): p. 81-106.
5. BMJ, Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients, *British Medical Journal*, 2002, 324(7329): p. 71-86.
6. Mehta, S.R., et al., Effects of pretreatment with clopidogrel and aspirin followed by long- term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study, *Lancet*, 2001, 358(9281): p. 527-33.
7. Steinhubl SR, Berger PB, Mann JT, 3rd, et al., Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial, *Journal of the American Medical Association*, 2002, 288:2411–2420.
8. Yusuf, S.Z., F.; Metha, S.R.; Chrolavicius, S.; Tognoni, G.; Fox, K.A., The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators, *New England Journal of Medicine*, 2001, 345: 494-502.
9. Victor L. Serebruany, Alex I. Malinin, Wendy Ziai, Alex N. Pokov, Deepak L. Bhatt, Mark J., Alberts and Dan F. Hanley,Effects of Clopidogrel and Aspirin in Combination Versus Aspirin Alone on Platelet Activation and Major Receptor Expression in Patients After Recent Ischemic Stroke : For the Plavix Use for Treatment of Stroke (PLUTO-Stroke) Trial, *Stroke*, 2005, 36:2289-2292.
10. Tang M, Y.M.M., Jian C N, Antipalet agents Aspirin and Clopidogrel are Hydrolysed by Distinct Hydroxylesterases and Clopidogrel is Transesterificated in the presence of ethyl alcohol. *Journal of Pharmacology and Experimental Therapeutics*, 2006, 319.
11. Purushotam K. Sinha, M.C.D.a.K.G.B., A Validated Stability Indicating HPTLC Method for Determination of Aspirin and Clopidogrel Bisulphate in Combined Dosage Form, *Eurasian Journal of Analytical Chemistry*, 2009, 4(2): 152-160.
12. Blair, T.C.; Buchton, G.; Breezer, A.E., Bloomfield, S.K. Intramolecular general base catalyzed ester hydrolysis, *International Journal of Pharmaceutics*, 1990, 63 (3), 257.
13. Sadeghnejad GR, York P, Stanley-Wood NG., Water vapor interaction with pharmaceutical cellulose powders, *Drug Development of Industrial Pharmacy*, 1986, 12:2171–2192. doi: 10.3109/03639048609042629.
14. Hageman MJ., The role of moisture in protein stability, *Drug Development of Industrial Pharmacy*, 1988, 14:2047–2070. doi: 10.3109/03639048809152002.
15. Leeson LJ, Mattocks AM, Decomposition of aspirin in thesolid state, *Journal of American Pharmaceutical Association,* 1957, 47:329–333.

16. Pharmamanufacturing, 2005, Moisture content in tablets, *http://www.pharmamanufacturing.com/experts/answers/2005/7.html* (accessed on 03/04/2013)
17. Pourkavoos N, Peck GE., Evaluation of moisture sorption by tablet cores containing superdisintegrants during the aqueous film coating process, *Pharmacy Research*, 1993, 10(8):1212-8.
18. Carstensen, J.T., Drug Effect of moisture on the stability of solid dosage forms, *Drug Development and Industrial Pharmacy*, 1988, 14: 1927-1969.
19. Cartensen, J.T., Van Scoik, K., Amorphous-to-crystalline transformation of sucrose, *Pharmacy Research*, 1990, 7(12):1278-81.
20. Zografi, G., States of water associated with solids, *Drug Development and Industrial Pharmacy*, 1988, 14:1905–1926.
21. Zografi, G.; Kontny, M.J., Yang, A.Y.S.; Brenner, G.S., Surface area and water vapor sorption of macrocrystalline cellulose, *International Journal of Pharmacy*, 1984, 18:99–116.
22. Mitrevej, A. (1982), A Comprehensive Study of Water Vapor Sorption by Aspirin-Disintegrant Blends and its Relationship to Aspirin Stability; Ph.D. Thesis.
23. Carstensen, J.T.; Attarchi, F., Decomposition of aspirin in the solid state in the presence of limited amounts of moisture II: Kinetics and salting-in of aspirin in aqueous acetic acid solutions, *Journal of Pharmaceutical Sciences*, 1998, 74 (4): 314-317.