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Formulation and development of aspirin / extended release dipyridamole capsules

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ABSTRACT

Aspirin plus extended-release Dipyridamole was superior to Clopidogrel in the prevention of recurrent stroke. Granular grade of Aspirin was used for product development. Opadry white YS-17027 was used to seal coat the Aspirin. Sugar is used for sugar coating purpose. Tartaric acid is an organic acid, is used as starter pellets of Dipyridamole for maintaining microenvironmental acidic pH for the drugs, Hypromellose was used as a film forming Polymers. Eudragit S100 is a Methacrylic acid copolymer, used for enteric coating. Aggrenox® (A1) Capsules marketed by Boehringer Ingelheim Pharma USA was selected as Innovator's Drug product. In vitro dissolution of Aspirin and Dipyridamole was carried out in 0.1N HCl followed by phosphate buffer pH5.5 using USP XXI basket apparatus. Increase in quantity of HPMC HP55, Eudragit S100 and Traicetine retard the release of Dipyridamole. Optimised formulation of Aspirin/Extended release Dipyridamole capsules were packed in a High wall thickness HDPE bottle with induction seal and with 9g silica gel and Medium wall thickness round HDPE bottle with cap containing Desiccant and additional desiccant 6g for conducting the laboratory stability studies.

Keyword: Aspirin, Dipyridamole, Wruster coating, Extended release.

INTRODUCTION

The antiplatelet agent aspirin is chemically known as acetylsalicylic acid. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary odor. It is highly lipid soluble and slightly soluble in water. Dipyridamole is an antiplatelet agent chemically described as 2,2',2",2"'-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]-tetraethanol. Dipyridamole is an odorless yellow crystalline substance, having a bitter taste. It is soluble in dilute acids, methanol and chloroform, and is practically insoluble in water. Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclooxygenase and thus inhibits the generation of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction. Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes *in vitro* and *in vivo*; the inhibition occurs in a dose-dependent manner at therapeutic concentrations (0.5−1.9 μ g/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A2-receptor thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3',5'-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor (PAF), collagen and adenosine diphosphate (ADP). Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. While the inhibition of cAMP-PDE is weak, therapeutic levels of Dipyridamole inhibit cyclic-3',5'- guanosine monophosphate-PDE (cGMP-PDE), thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, now identified as nitric oxide).[1-3]

Aspirin has been shown to reduce the risk of stroke recurrence by about 23% as compared with placebo. Studies of Clopidogrel have suggested an 8% relative risk reduction of stroke recurrence, as compared with aspirin, among stroke patients, whereas studies of aspirin plus extended-release Dipyridamole have suggested relative risk reductions of 20 to 23% as compared with aspirin alone.[4-5] Indirect comparisons suggested that aspirin plus extended-release Dipyridamole was superior to Clopidogrel in the prevention of recurrent stroke.14

The aim of the formulation development work was to develop stable formulation of Aspirin /extended release Dipyridamole Capsules. Development work was concentrated on the production of aesthetically as well as pharmaceutically acceptable Capsules that could be manufactured using the available technology and that would be stable in the proposed packs over the proposed shelf life.

MATERIALS AND METHODS

Material: Aspirin and Dipyridamole obtained as gift sample from Shreya Life Sciences Pvt.Ltd. Aurangabad. The excipients used for the development batches were selected based upon formulation information generated from the literature. The excipients are all of pharmacopoeial grades and are routinely used in the pharma industry for the manufacturing of hard gelatin capsules.

Methods

Physical characteristics of the Innovator's Drug product (Aggrenox®) for following parameters i.e. Description, Avg. Fill Wt. Capsule size and Packaging material.

I. Aspirin Part:[6-7]

Seal Coat: Opadry white YS-17027 was dispersed in Isopropyl alcohol and then Methylene chloride was added to it under stirring. The solution was stirred for 45 mins. Solution was strained using 80# sieve. Aspirin (Granular grade) was sifted through 18 # sieve and transferred to fluidized bed processor bowl fitted with Wurster column (bottom spray), granules were seal coated using above solution. The granules were dried in a Fluid Bed Processor and sized using 16 # sieve and 40 # sieve.

Sugar coat: The sugar coating solution was made by dissolving the Sugar, Methyl Paraben Propyl Paraben in purified water heated to 90-95 °C. Seal coated granules were sugar coated using the above solution. Sugar- coated granules were dried and sized using 16# sieve and 40 # sieve.

Gloss coat: Opaglos 6000P solution was diluted with Isopropyl alcohol and sprayed onto the sugar coated granules.

II. Dipyridamole pellets:[6-7]

Tartaric acid pellets : Sugar Spheres, NF were coated using tartaric acid solution along with the Hydroxypropyl cellulose (Klucel LF) in purified water using Fluid bed Processor fitted with the wurster coating column (bottom spray). Tartaric acid pellets were dried and sized.

Seal coating: Tartaric acid pellets were seal coated using Opadry orange 04k53924 nonaqueous solution.

Dipyridamole drug suspension: Hydroxypropyl Cellulose was dissolved in Isopropyl Alcohol, followed by addition of Dipyridamole with continuous stirring.

Drug loading: Seal coated tartaric acid pellets were sprayed with the above drug suspension in Fluid Bed processor fitted with Wurster column (Bottom spray). Drug loaded pellets were dried and sized using 16 # sieve and 30# sieve.
Over coating: Drug loaded pellets were overcoated using Hypromellose and HPC non-aqueous solution. Overcoated pellets were dried and sized using 16 # sieve and 30# sieve.

Enteric coating: Enteric coating solution was prepared by addition of Hydroxypropyl Methylcellulose Phthalate (HP-55) in Isopropyl Alcohol and Methylene Chloride mixture, followed by addition of Eudragit S100 and Triacetin. This solution was sprayed onto the overcoated pellets using Fluid bed processor fitted with the Wurster column (bottom spray).

Enteric- coated pellets were dried and sized using 16# sieve and 30# sieve.

Capsule filling: Aspirin granules and Dipyridamole pellets were filled manually into the capsules.

Table No. 1 Composition of laboratory batches

Sr. No.	Ingredient	Qty (mg)/Capsule F1	Qty (mg)/Capsule F2	Qty (mg)/Capsule F3
A	**ASPIRIN PELLETS**			
I	**Seal Coating**			
1	Aspirin (Granular)	25	25	25
2	Opadry YS-17027 white	5	5	5
3	Isopropyl alcohol *	q.s.	q.s.	q.s.
4	Methylene chloride **	q.s.	q.s.	q.s.
II	**Sugar Coating**			
1	Sugar	11.97	11.97	11.97
2	Methyl Paraben	0.024	0.024	0.024
3	Propyl Paraben	0.006	0.006	0.006
4	Talc	2	2	2
5	Water***	q.s.	q.s.	q.s.
III	**Gloss Coating**			
1	Opaglos 6000P dispersion equivalent to solid	1	1	1
2	Isopropyl alcohol*	q.s.	q.s.	q.s.
	Total weight of Part A	**45**	**45**	**45**
B	**DIPYRIDAMOLE PELLETS**			
I	**Tartaric Acid Loading**			
1	Sugar spheres 30/35 #	100	100	100
2	Tartaric Acid	210	210	210
3	Klucel LF (Hydroxy PropylCellulose)	10	10	10
4	Water ***	q.s.	q.s.	q.s.
II	**Seal Coating**			
5	Opadry orange 04k53924	20	20	20
6	Isopropyl Alcohol *	q.s.	q.s.	q.s.
7	Methylene Chloride **	q.s.	q.s.	q.s.
III	**Dipyridamole loading**			
8	Dipyridamole	200	200	200
9	Klucel LF (Hydroxy PropylCellulose)	25	25	25
10	Talc	5	5	5
11	Isopropyl Alcohol *	q.s.	q.s.	q.s.
IV	**Over Coating**			
12	Hypromellose E - 15	7.5	7.5	7.5
13	Klucel LF (Hydroxy PropylCellulose)	7.5	7.5	7.5
14	Triacetin	2	2	2
15	Talc	3	3	3
16	Isopropyl alcohol	q.s.	q.s.	q.s.
17	Methylene Chloride	q.s.	q.s.	q.s.
V	**Enteric Coating**			
18	Hypromellose phthalate (HPMC HP 55)	3.75	4.5	7.5
19	Methacrylic acid Copolymer (Eudragit S100)	8.75	10.5	17.5
20	Triacetin	1.5	1.8	3.0
21	Talc	1	1.2	2
22	Isopropyl Alcohol *	q.s.	q.s.	q.s.
23	Methylene chloride **	q.s.	q.s.	q.s.
	Total weight of part B	**605**	**608**	**620**
	Total fill weight (Part A + Part B)	**650**	**653**	**665**
24	White opaque hard gelatin capsules	118	118	118
25	Total average weight (filled Capsule)	768	771	783

, **, * Removed during drying. Appears only in traces in final product*

***In Vitro* dissolution:** Dissolution studies were performed using USP XXI basket apparatus (Lab India 2000) at 100 rpm in 0.01N HCL for 1 hour, followed by pH5.5 phosphate buffer thereafter. Temperature was maintained at 37 ± 0.5^{o}C. Sample 5mL was withdrawn at predetermined time intervals and replaced with fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45µm and analyzed by using UV spectrophotometer (UV 1700, Shimadzu, Japan).

In vitro dissolution of Dipyridamole was also carried out in 0.1N HCl and phosphate buffer pH5.5 using USP XXI basket apparatus at 100 rpm.[8]

Packaging material: Aspirin/Extended release Dipyridamole capsules were packed in a High wall thickness (about 1mm) HDPE bottle with induction seal and with 9g silica gel and Medium wall thickness round HDPE bottle with cap containing Desiccant and additional desiccant 6g for conducting the laboratory stability studies. The laboratory

stability data suggest the use of high wall thickness (about 2mm) HDPE bottle with in-built desiccant in cap, similar to Innovator's product packing material that needs to be used.[9]

Stability Studies: Batches those were manufactured using the active ingredient, Aspirin & Dipyridamole Capsules (F1) using typical manufacturing laboratory scale equipments were kept on stability at 40°C ± 2°C / 75% ± 5%RH (Accelerated conditions) for 3month.[10]

Result and Discussion: Innovator's Drug product, Aggrenox® (A1) Capsules marketed by Boehringer Ingelheim Pharma USA was evaluated for various physical parametes viz. description, capsule size, avg.fill wt. and packaging material. (Table no.2)

Table 2: Physical characteristics of the Innovator's Drug product (Aggrenox®)

Parameters	25 mg/200mg
Description	Red and ivory colored Hard gelatin capsules filled with extended release pellets incorporating Dipyridamole and a round white tablet incorporating immediate release Aspirin, imprinted with Boehringer Ingelheim logo and with '01A'.
Avg. fill wt. (mg)	116mg + 586mg
Capsule Size	'0'
Pack profile	Round shaped, white opaque HDPE container of 38mm neck finish with child resistant closure with in-built desiccant.

For Aspirin granules
Granular grade of Aspirin was used for product development. Opadry white YS-17027 was used to seal coat the Aspirin. Sugar is used for sugar coating purpose. Methyl Paraben and Propyl Paraben are used as preservatives and Opaglos 6000P is used for polishing the granules.[7]

For Dipyridamole Pellets:
Sugar Spheres, NF are used for drug loading purpose in case of pellets. Tartaric acid is an organic acid, is used as starter pellets which is used to have a microenvironmental acidic pH for the drugs, which are soluble only in acidic pH. Hypromellose and Hydroxypropyl Cellulose are used as a film forming Polymers. Eudragit S100 is a Methacrylic Acid copolymer, which is used for enteric coating, which dissolves in pH above 7.0. Hypromellose Phthalate (HP-55) is also used as an enteric coating polymer, which dissolves in pH above 5.5.[7]

***In Vitro* dissolution:** The *in vitro* dissolution study of Aspirin /extended release Dipyridamole Capsules were performed using USP XXI (Basket Apparatus) at 100 rpm in 0.01N HCL for 1 hour, followed by pH5.5 phosphate buffer thereafter.(Fig.1-4) Based on *in vitro* dissolution studies it is clear that Aspirin is completely released within 1hr from each formulation, while extended release pattern was observed in case of Dipyridamole. Increase in quantity of HPMC HP55, Eudragit S100 and Triacetin retard the release of Dipyridamole from pellets.[4-5] Formulation F1which contain low quantity HPMC HP55, Eudragit S100 and Triacetin showed faster release of Dipyridamole in comparison with Formulation F2 and F3 containing high quantity of HPMC HP55, Eudragit S100 and Triacetin. Thus formulation F1 is selected for further research work.

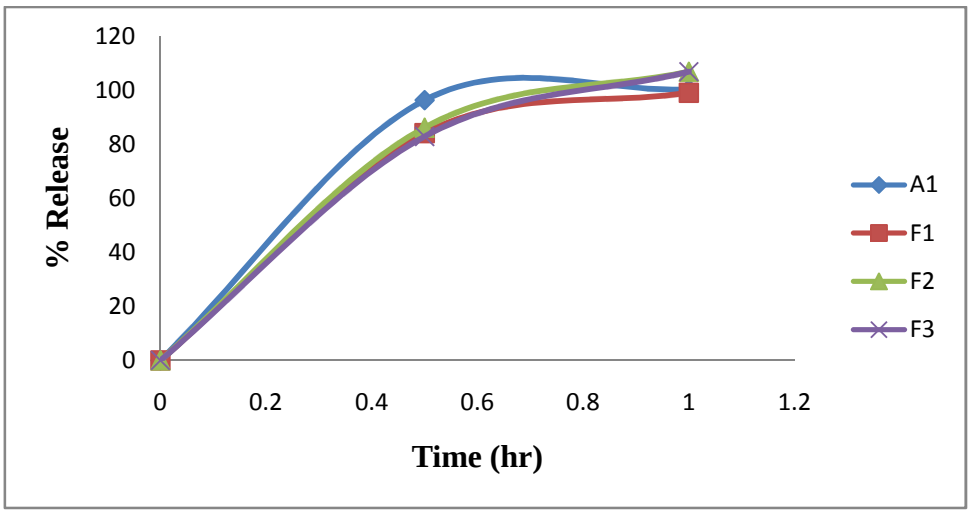

Figure 1. Comparative dissolution in 0.01N HCL for Aspirin

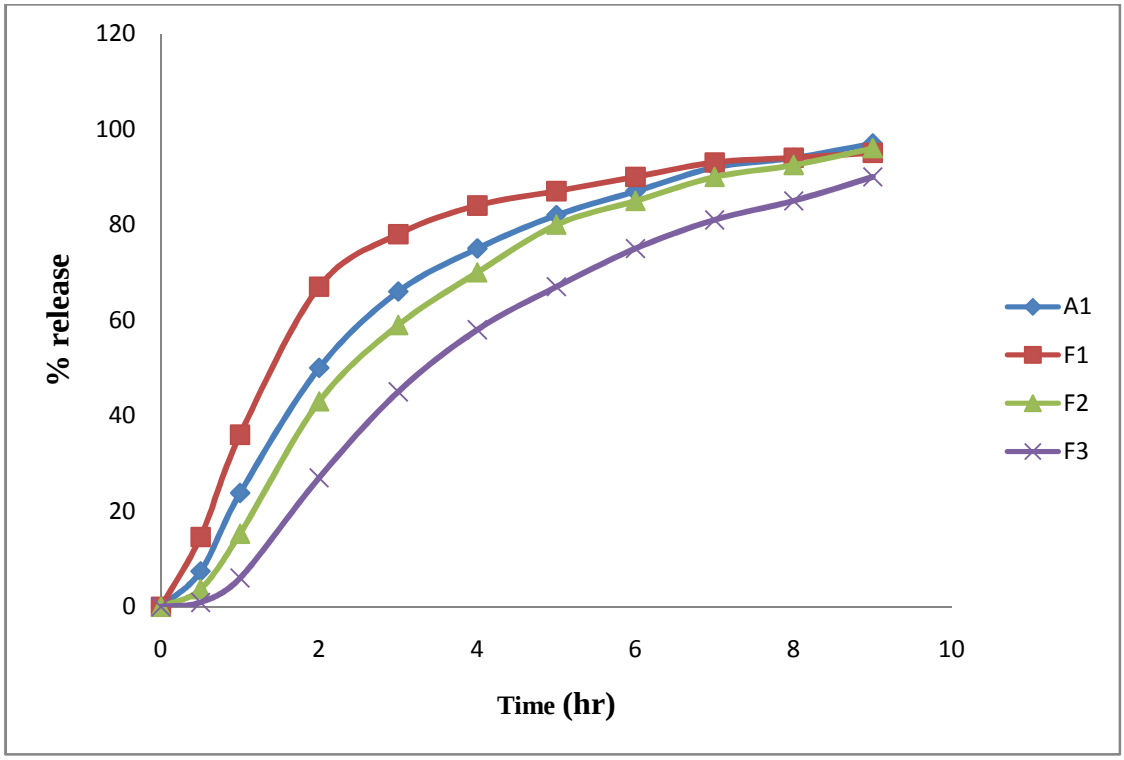

Figure 2.Comparative dissolution in 0.01 N HCl followed by pH 5.5 phosphate buffer for Dipyridamole.

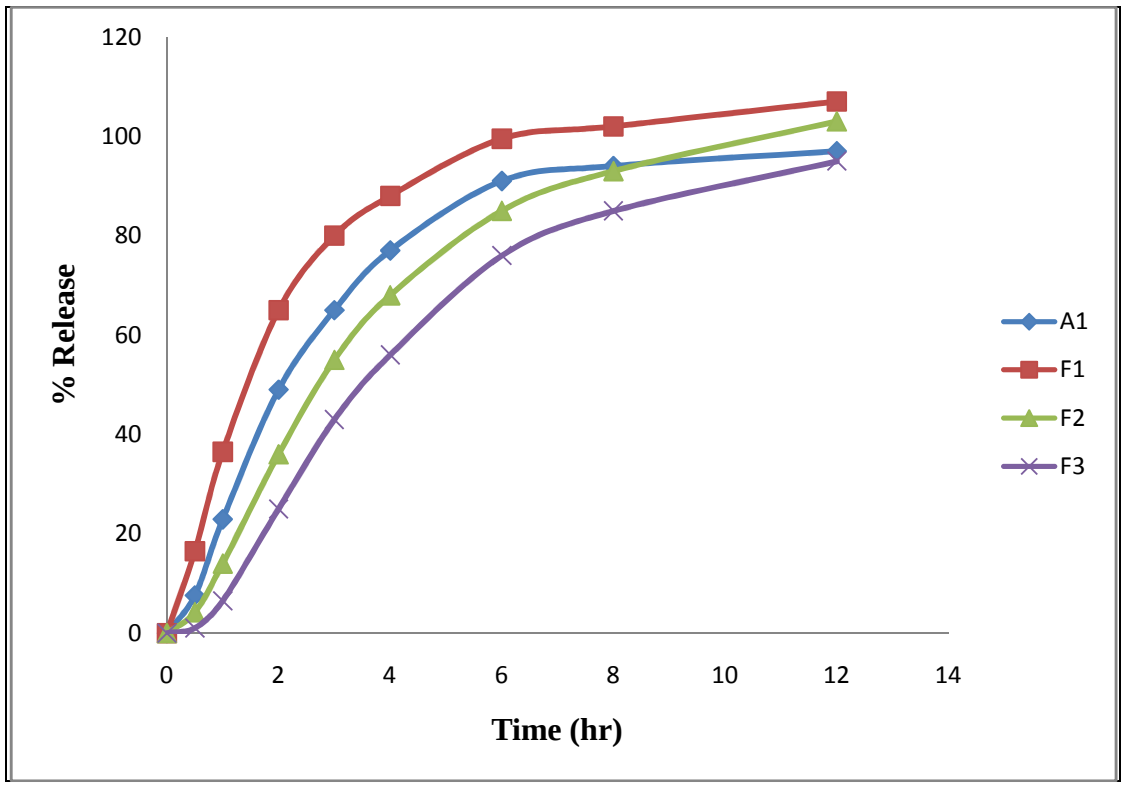

Figure 3. Comparative dissolution in 0.1 N HCl for Dipyridamole.

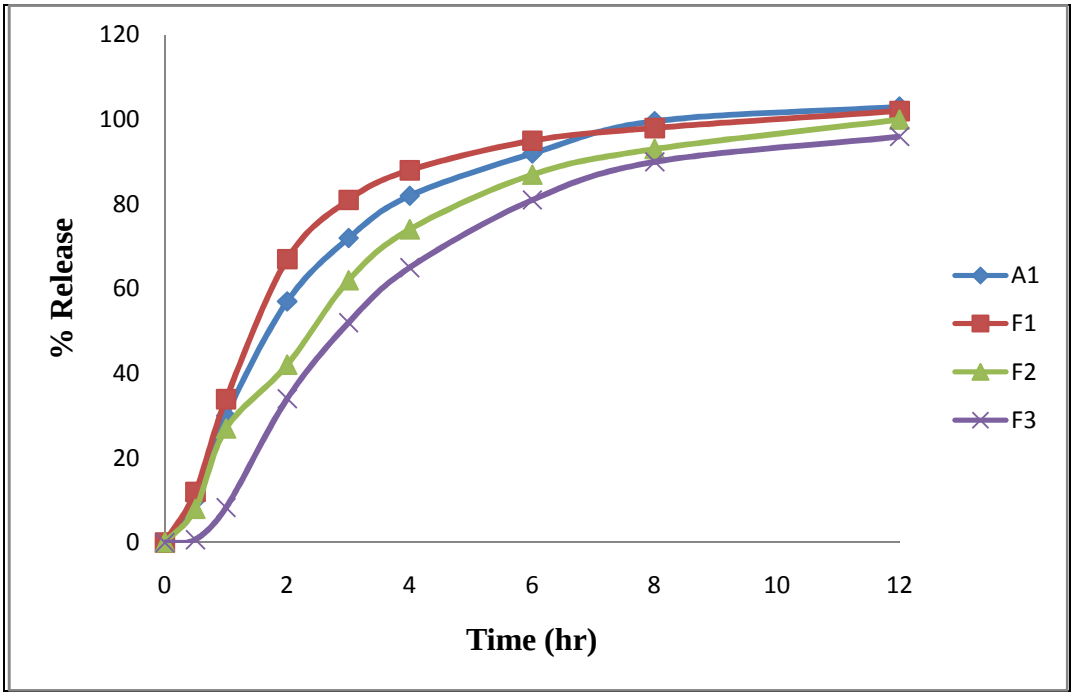

Figure 4.Comparative dissolution in pH 5.5 phosphate buffer for Dipyridamole.

Container Closure System

The Innovator pack profile is Round shaped, white opaque HDPE container of 38mm neck finish with child resistant closure with in-built desiccant. Aspirin/Extended release Dipyridamole capsules were packed in a High wall thickness (about 1mm) HDPE bottle with induction seal and with 9g silica gel and Medium wall thickness round HDPE bottle with cap containing Desiccant and additional desiccant 6g for conducting the laboratory stability studies.

Stability Studies

From stability study data indicate there is no significant change in dissolution profile of Dipyridamole when store in High wall thickness HDPE bottle with 6g silica gel (with induction seal) and HDPE bottle with Inbuilt desiccant in Cap (4g) and additional 6 g silica gel. While Dissolution profile of aspirin was significantly affected when store in High wall thickness HDPE bottle with 6g silica gel (with induction seal). Therefore use of high wall thickness (about 2mm) HDPE bottle with in-built desiccant in cap, similar to Innovator's product packing material needs to be used.

Table 3. Dissolution profile of stability samples in 0.01NHCL, followed by pH5.5 phosphate buffer for Dipyridamole

Time (hr)	Batch no. F1		Batch no. F1	
	High wall thickness HDPE bottle with 9g silica gel (with induction seal)		HDPE bottle with In-built desiccant in Cap(4g) and additional 6 g silica gel	
	Initial	3 Months 40°C/75% RH	Initial	3 Months 40°C/75% RH
0.5	14.6	13.3	14.6	13.3
1	36.2	33.4	36.2	35.6
2	67.6	63.1	67.6	66.9
3	78.3	75.4	78.3	77.8
4	84.9	82.2	84.9	84.2
5	87.1	84.4	87.1	86.4
6	90.3	88.5	90.3	90.0
7	93.2	90.1	93.2	93.3
8	94.7	92.6	94.7	94.3
9	95.0	93.1	95.0	94.9

Table 4. Dissolution profile of stability samples in 0.01NHCL, followed by pH5.5 phosphate buffer for Aspirin

Time (hr)	Batch no. F1		Batch no. F1	
	High wall thickness HDPE bottle with 9g silica gel (with induction seal)		HDPE bottle with In-built desiccant in Cap(4g) and additional 6 g silica gel	
	Initial	3 Months 40°C/75% RH	Initial	3 Months 40°C/75% RH
1	99.1	85.8	99.1	91.9

REFERENCES

[1] Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS. *Neurology* **2006**;66:641-646.
[2] Gent M, Blakely JA, Easton JD, *et al*. *Lancet*. **1989**;1:1215-1220.
[3] Hass WK, Easton JD, Adams HP Jr, *et al*. *N Engl J Med* **1989**;321:501-507.
[4] CAPRIE Steering Committee. *Lancet* **1996**;348:1329-1339.
[5] Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. *J Neurol Sci* **1996**; 143:1-13.
[6] Chien YW. Novel drug delivery system: Fundamental development concept, Biomedical assessment. 1st edition. Marcel Dekker Inc; **2001**; 126-132.
[7] Ghebre Sellasie. A general overview- pharmaceutical technology. 1st edition. Marcel Dekker Inc.; **1989**;45-56.
[8] Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* **2002**;324:71-86.
[9] Hervey PS, Goa KL, Extended-release dipyridamole/aspirin, *Drugs*, **1999**;58(3):469–475.
[10] International Conference on Harmonization (ICH) Topic Q 1 A (R2) Stability Testing of new Drug Substances and Products, **2003**.