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RESEARCH ARTICLE

Formulation and Stabilization of Aspirin Mini-Tablets with the Aid of Weak Acid and Moisture Protective Coating

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ABSTRACT

The main objective of the present study is to formulate a stable aspirin mini tablet with the aid of a weak acid in core tablet & coated with non aqueous moisture protective coating. Aspirin is highly unstable at alkaline environment & and prone to undergo degradation by hydrolysis. The pre-formulation study reveals, Aspirin is incompatible with alkali salts, and aspirin itself degrades at exposure condition of elevated temperature and humidity. Whereas, with weak acids, the stability of aspirin is comparatively better. Hence, a weak acid is selected in core tablet. To control the impact of humidity on degradation, a moisture protective layer is coated on core tablet with non aqueous solvent, using conventional coating pan. The coated mini tablets are encapsulated in a hard gelatin capsule shell. The filled capsules are evaluated for description, assay, dissolution, water by KF at initial and 3months accelerated condition (40 ± 2°C/75± 5%RH), and to conclude the quantity of weak acid & percentage of moisture protective coating required to stabilize the formulation. The formulation with 4mg & 6mg/unit of alginic acid/unit and 4% film coating are failed in stability. The formulation with 8mg/unit of alginic acid & 6% moisture protective coating was found to be stable, and the degradation was controlled.

KEYWORDS

Dissolution**,** Aspirin, Mini-tablets, Alginic acid, moisture protective coating

INTRODUCTION

Aspirin (Acetylsalicylic acid) belong to class of drug referred to as Non- steroidal anti-inflammatory drugs, it's clinically useful as analgesics, anti-inflammation, antipyretic, anti-thrombolytic and anti-rheumatic[1]. Aspirin also has an antiplatelet effect by inhibiting the production of thromboxane, which under normal circumstances binds platelet molecules together to create a patch over damaged walls of blood vessels.

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Because the platelet patch can become too large and also block blood flow, locally and downstream, aspirin is also used long-term, at low doses, to prevent heart attacks, strokes, and blood clot formation in people at high risk for developing blood clots[2]. It has also been established that low doses of aspirin may be given immediately after a heart attack to reduce the risk of another heart attack or of the death of cardiac tissue[3]. Aspirin undergoes degradation by hydrolysis. The hydrolysis is catalyzed mainly by alkali, heat in presence of moisture. Aspirin is more stable at pH 3.7 (pKa value of aspirin = 3.7). Degradation of aspirin is aimed

to controlled by maintain the product's pH value in line with pKa value of aspirin, with the aid of weak acids. Pellets and mini tablets have gained importance over the years due to their distinctive advantages in both technological and therapeutic aspects. Aspirin In case of aspirin[4,5], direct compression technique has been employed to compress the tablet, because the powder is highly moisture sensitive.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received: Aspirin (Rhodine, Thailand), Alginic acid (kelacid)(FMC, Europe), Opadry AMB white 80W68912 (colorcon, India), Silicon dioxide (syloid 244 FP)(Grace division, USA), Microcrystalline cellulose (Avicel PH 112) (FMC ,USA), Lactose Anhydrous (Supertab 21AN) (DFE pharma, USA), Stearic acid (Merck, Europe), Talc (Luzenac, Italy), pregealtinised starch (Starch 1500, Dow, USA), Isopropyl alcohol and methylene chloride was procured from RFCL Limited., New Delhi, India. All chemicals were reagent grade or higher.

Digital weighing balance (C-220) (make: Saritorious), Mechanical sifter with the screens of ASTM 40# & ASTM 60#, Octagonal blender 4L (Sams tech, India), 16 station rotary compression machine (Cadmach, India), conventional coating pan(a Remi mechanical propellant stirrer (RA124) (make:Remi), Manual capsule filling machine (MAC 300) (make: Pam machineries), Tray drier (make : Ganson eng.), double beam UV Visible spectrophotometer (make: schimadzu), Dissolution test apparatus (Electrolab).

Methods

Drug-Excipient Polymer Compatibility Study

Aspirin is individually mixed with different excipient, sifted through ASTM 40#, loaded in to 40±2°C/75±5%RH accelerated chamber and exposed for four weeks. Samples are withdrawn after 2 weeks and 4 weeks. The physical admixture of the samples exposed are evaluated at Initial, 2 weeks and 4 weeks at exposed condition for Description & Assay

Table 1: Aspirin and Excipients Compatibility Study

Drug + Excipients	Ratio
Aspirin (D)	-
D + Microcrystalline cellulose (Avicel PH112)	1 : 1
D + Lactose anhydrous (Supertab 21AN)	1 : 1
D + Corn starch (PURE DENT B700)	1 : 0.5
D + Pregelatinised starch (Starch 1500)	1 : 0.5
D + Alginic acid (Kelacid)	1 : 0.1
D + Silicon dioxide (Syloid 244 FP)	1 : 0.5
D + Talc	1 : 0.2
D + Stearic acid	1 : 0.1
D + Opadry AMB white 80W50612	1 : 0.2

Preparation of Mini-Tablets[6]

Formulation of Aspirin mini tablets involves 3 stages

a) Stage – I : Blending

b) Stage - II : Compression

c) Stage - III : Film coating

Stage –I Blending

- Aspirin was co-sifted with Advice and lactose through ASTM 40#.
- Alginic acid was co-sifted with pregel starch through ASTM 60#.
- Syloid and Talc was sifted through ASTM 60#.
- The above sifted materials was loaded in octagonal blender and mixed for 15 minutes at 15 rpm.

Table 2: Composition of Aspirin Film Coated Mini-Tablets

S.No	Ingredients	F1	F2	F3	F4
1	Aspirin (Rhodine 2080A)	75	75	75	75
2	Corn starch NF	12	12	12	12
3	Alginic acid	4	6	8	10
4	Lactose anhydrous (Supertab 21 AN)	25	23	21	19
5	Microcrystalline cellulose (Avicel PH112)	38	38	38	38
6	Silicon dioxide (Syloid 244FP)	2	2	2	2
7	Talc	2	2	2	2
8	Stearic acid	2	2	2	2
	Sub total	**160**	**160**	**160**	**160**
Film coating					
S.No	**Ingredients**	**F-1A**	**F-2A**	**F-3A**	**F-4A**
1	Opadry AMB white	6.4	6.4	6.4	6.4
2	Methylene chloride	qs	qs	qs	qs
3	Isopropyl alcohol	qs	qs	qs	qs
	Sub total	**166.4**	**166.4**	**166.4**	**166.4**
S.No	**Ingredients**	**F-1B**	**F-2B**	**F-3B**	**F-4B**
1	Opadry AMB white	9.6	9.6	9.6	9.6
2	Methylene chloride	qs	qs	qs	qs
3	Isopropyl alcohol	qs	qs	qs	qs
	Total	**169.6**	**169.6**	**169.6**	**169.6**
S.No	**Ingredients**	**F-1C**	**F-2C**	**F-3C**	**F-4C**
1	Opadry AMB white	12.8	12.8	12.8	12.8
2	Methylene chloride	qs	qs	qs	qs
3	Isopropyl alcohol	qs	qs	qs	qs
	Total	**172.8**	**172.8**	**172.8**	**172.8**

Table 3: In-Process Parameters at Various Steps

Parameters	Compression	Coating
Description	White to off-white circular biconvex mini tablets	White to off-white circular biconvex mini tablets
Uniformity of tablet weight	20mg ± 2mg	Target weight ± 10%
Hardness (N)	10-20N	20-40N
Thickness (mm)	3.1- 3.5mm	3.1- 3.5mm
Disintegration time	NMT 15 min	NMT 15 min

- Stearic acid was sifted through ASTM 60# and loaded in octagonal blender and mixed for 5 minutes at 15 rpm.
- Each formula was having the batch size of 4000 units.

Stage –II Compression

- The lubricated blend was compressed using 2.5mm multi-tip punch with the target weight of 20mg/unit and 8 units/unit dose.
- The compressed mini-tablets were evaluated for hardness, thickness and disintegration time.
- The lot size for barrier coating was 4000 units.

Stage-III: Film coating

- Opadry AMB white 80W50612 suspended in Isopropyl alcohol and methylene chloride admixture under stirring.
- Stirring for continued for 30 minutes.
- The resultant suspension was coated on compressed mini-tablets with different percentage weight gain by using conventional coating pan.
- During the preparation of coating solution the 10% of excess was prepared to recover the loss during practical work. And the coating solution was sprayed over barrier coated pellets using Fluid bed coater until weight gain was achieved and % yield was calculated.
- The solid content of film coating suspension was 7% w/w.

Encapsulation

The coated mini-tablets were filled in to size "0" hard gelatin capsules, and evaluated for assay and dissolution.

Cured for 2 hrs using tray drier, at 50°C.

The cured pellets were Note: Top coated pellets were used for direct exposure study, and filled capsules were loaded on stability as per ICH requirements.

Stability Study[10]

Stability testing of drug products begins as a part of drug discovery and ends with the emise of the compound or commercial product. FDA and ICH specify the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. The ICH Guidelines have established different temperatures and period of stability testing. The top coated pellets of formulation TE-1 to TE-6 were filled in size'1'capsules, packed in HDPE bottle, and loaded on stability chamber as per ICH guidelines, as mentioned in table-4.

Table 4: ICH guidelines for Stability Study

Study Storage	Condition	Time
Long term	25°C±2°C / 60% RH±5% RH	12 month
Intermediate	30°C±2°C /65% RH±5% RH	12 months
Accelerated	40°C±2°C /75% RH±5% RH	6 months

To evaluate the impact of barrier coating in short period, the product is evaluated at accelerated stability condition.

Evaluation of Aspirin Film Coated Mini Tablets

Uniformity of Tablet Weight Test[8]

Ten capsules from the batch were randomly selected, individual weight of the selected representative was determined using a digital electronic balance. The average tablet weight and the standard deviation from the mean were calculated.

Capsule Disintegration Test[8]

Six capsules randomly selected were introduced into the six baskets of the disintegration testing apparatus (Electrolab, India). The disintegrating medium was de ionized water maintained at 37°c + 1.0°c. The time taken for each capsule to disintegrate to break up into a smaller units and passes through the screen mesh orifices at the bottom of the basket was recorded.

Dissolution [9, 10]

Acetate buffer at pH 4.5 was used as the dissolution medium as specified in the British Pharmacopoeia. It was prepared by mixing 29.9 g of sodium acetate with 16.6 mL of glacial acetic acid and sufficient distilled water to produce 10 L. Sodium acetate and glacial acetic acid were analytical grade and purchased from Sigma–Aldrich UK. Pure aspirin powder (Acetylsalicylic Acid BP, Sigma– Aldrich UK) was dissolved in the acetate buffer to make a series of standard calibration solutions with different concentrations for development of a calibration curve using a UV spectrophotometer at 265 nm. Dissolution Testing In vitro dissolution was carried out via USP Apparatus 2 (paddle) at a speed of 75 rpm in 900 mol of dissolution medium (pH 4.5 acetate buffer) maintained at 37 ± 0.5 °C using a water bath fitted with a variable- speed stirrer and heater (Erweka DT6). Selection of 75- rpm rotation speed was based on the British Pharmacopoeia guideline (22). Samples (5 ± 0.1 mL) were taken manually at 10, 20, 30, 45, 60, and 90 min and replaced with the samples were filtered, and the absorbance was measured at 265 nm using a UV spectrophotometer (PU 8625 UV/VIS spectrophotometer). The drug concentration determined by the calibration model was used to calculate the total mass of the drug released in the medium. In this work, the dissolution profiles are represented as the cumulative percentages of the amount of drug released at each sampling interval. Each profile is the average of six individual tablets.

Assay[8]

Aspirin film coated mini-tablets from the capsule were dispersed in to 190 ml of pH 6.8 phosphate buffers by ultra-sonication for 30 minutes followed by 10 minutes stirring using magnetic stirrer. The solution was then filtered and the residues over filter paper were washed with 10 ml phosphate buffer. The solution was then diluted up to suitable concentration and absorbance was measured using double beam UV-VIS Spectrophotometer at 289 nm.

RESULTS AND DISCCUSION

Drug-Excipient Compatibility Study

The Drug – Excipient compatibility study is conducted for assay and description, the results are tabulated in Table 5.

Table 5: Drug – Excipients compatibility study

Drug : Excipient	Ratio	Initial		2 Week 40 ±2°C/75±5%RH		4 Week 40/75 40 ±2°C/75±5%RH	
		Description	Assay	Description	Assay	Description	Assay
Aspirin (D)	-	White to off white powder	99.6	Off white powder	98.7	Off white to pale pink powder	93.5
D + Microcrystalline cellulose (Avicel PH112)	1 : 1	Off - white powder	101.1	pale pink colored powder	95.8	pale pink colored powder	91.2
D + Lactose anhydrous (Supertab 21AN)	1 : 1	Off - white powder	99.9	pale pink colored powder	96.5	pale pink colored powder	92.1
D + Corn starch (PURE DENT B700)	1 : 0.5	Off - white powder	101.1	pale pink colored powder	95.8	pale pink colored powder	92.1

D + Pregealtinised starch (Starch 1500)	1 : 0.5	Off - white powder	99.6	pale pink colored powder	98.5	pale pink colored powder	93.6
D + Alginic acid (Kelacid)	1 : 0.2	Off - white powder	100.2	Off white powder	99.8	Off white powder	99.7
D + Silicon dioxide (Syloid 244 FP)	1 : 0.5	Off - white powder	99.6	pale pink colored powder	97.5	pale pink colored powder	94.3
D + Talc	1 : 0.2	Off - white powder	99.9	Off white powder	97.6	Off white to pale pink powder	95.2
D + Stearic acid	1 : 0.1	Off - white powder	100.2	Off white powder	97.5	Off white to pale pink powder	95.3
D + Opadry AMB white	1: 0.2	Off - white powder	100.3	Off white powder	96.5	Off white to pale pink powder	94.3

The results of compatibility study reveal that the drug is not stable at exposed condition as alone and with excipient. But the same was stabilized using alginic acid. Around 5-8% drop in potency is observed after 4 week direct exposure. Hence, a moisture protective layer and alginic acid is required to stabilize aspirin.

Physical Characterization of Aspirin Mini-Tablets Filled in Capsules

Table 6: Physical Characterization of Aspirin mini-tablets filled in capsules

Parameters	**Specification**	**Batch Number**			
		F1A	**F2A**	**F3A**	**F4A**
Number of mini-tablets per capsule	8	8	8	8	8
Uniformity of tablet weight	Mean ± SD	20.9 ± 0.10	20.8 ± 0.08	20.8 ± 0.12	20.8 ± 0.09
Disintegration time	NMT 15 min	4min 20 sec	3 min 45 sec	3 min 35 sec	3 min 15 sec
Parameters	**Specification**	**Batch Number**			
		F1B	**F2B**	**F3B**	**F4B**
Number of mini-tablets per capsule	8	8	8	8	8
Uniformity of tablet weight	Mean ± SD	21.2 ± 0.13	21.3 ± 0.08	21.2 ± 0.10	21.2 ± 0.07
Disintegration time	NMT 15 min	5min 5sec	4 min 35 sec	4min 25sec	4min 45 sec
Parameters	**Specification**	**Batch Number**			
		F1C	**F2C**	**F3C**	**F4C**
Number of mini-tablets per capsule	8	8	8	8	8
Uniformity of tablet weight	Mean ± SD	21.7 ± 0.10	21.7 ± 0.07	21.6 ± 0.11	21.7 ± 0.07
Disintegration time	NMT 15 min	5min 30 sec	4min 55 sec	4min 50 sec	5min 10sec

Physical Description of Mini-Tablets Filled in Capsules

Table 7: Comparison of physical description of Aspirin Mini-tablets filled in capsules 75mg (Initial Vs 3 months 40 ± 2°C/75 ± 5% RH)

Batch Number↓	Physical Description	
	Initial	**3 months 40 ± 2°C/75 ± 5% RH**
ASCL-C-F1A (4mg alginic acid + 4% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	pale pink colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F1B (4mg alginic acid + 6% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	Pale pink colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F1C (4mg alginic acid + 8% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	pale colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F2A (6mg alginic acid + 4% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	pale colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F2B (6mg alginic acid + 6% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	Pale colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F2C (6mg alginic acid + 8% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	Pale colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F3A (8mg alginic acid + 4% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	White to off white colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F3B (8mg alginic acid + 6% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	White to off white colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F3C (8mg alginic acid + 8% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	White to off white colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F4A (10mg alginic acid + 4% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	White to off white colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F4B (10mg alginic acid + 6% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	White to off white colored mini tablets filled in size"0" hard gelatin capsules
ASCL-C-F4C (10mg alginic acid + 8% film coating)	White to off white colored mini-tablets pellets filled in size"0" hard gelatin capsules	White to off white colored mini tablets filled in size"0" hard gelatin capsules

Results indicated that Batches F3A, F3B, F3C, F4A, F4B & F4C are not having any change in physical description in 3 months accelerated condition. F1A, F1B, F1C, F2A, F2B & F2C were failed in physical description at 3 months accelerated condition. From the results it was concluded that minimum 8mg alginic acid is required to have stable formulation.

Drug Content

Initial and Accelerated stability samples of the filled capsules were evaluated for Drug content & acid resistance. The results are tabulated in Table 8.

Table 8: Assay, Water by KF and Dissolution: (Initial Vs 3M Accelerated condition)

Batch Number↓	Initial			3M Accelerated condition		
	Assay	**Water by KF**	**Dissolution**	**Assay**	**Water by KF**	**Dissolution**
Limit	**90-110% of Label claim**	**NMT 4% w/w**	**NLT 80%(Q) in 30 min**	**90-110% of Label claim**	**NMT 4% w/w**	**NLT 80%(Q) in 30 min**
F1A	100.2 ± 0.36	1.25	93 ± 2.1	90.7 ± 0.67	5.6	62 ± 0.6
F2A	100.4 ± 0.2	1.42	97 ± 2.1	91.5 ± 0.66	4.8	62 ± 0.6
F3A	99.8 ± 0.25	1.5	96 ± 1.5	97.1 ± 0.53	2.8	90 ± 1.2
F4A	99.9 ± 0.35	1.52	96 ± 0.6	98.3 ± 0.23	3.2	85 ± 2.1
F1B	100.7 ± 0.81	1.32	93 ± 3.8	90.2 ± 0.81	3.1	63 ± 1.7
F2B	100.5 ± 0.25	1.25	96 ± 1.5	91.7 ± 0.35	3	76 ± 2.0
F3B	100.5 ± 0.06	1.24	97 ± 1.2	99.2 ± 0.15	1.9	92 ± 1.5
F4B	100.7 ± 0.12	1.25	99 ± 1.0	96.5 ± 0.1	1.85	89 ± 1.0
F1C	100.7 ± 0.5	1.25	96 ± 2.0	92.6 ± 0.12	2.8	69 ± 1.5
F2C	100.3 ± 1.19	1.32	98 ± 1.5	96.7 ± 0.17	2.4	77 ± 1.2
F3C	100.3 ± 0.42	1.22	98 ± 1.5	99.1 ± 0.15	1.85	90 ± 1.2
F4C	100.5 ± 0.06	1.2	96 ± 2.1	98.3 ± 0.2	1.9	87 ± 1.2

*Listed value indicates mean value of results and Standard deviation (Where n=3)

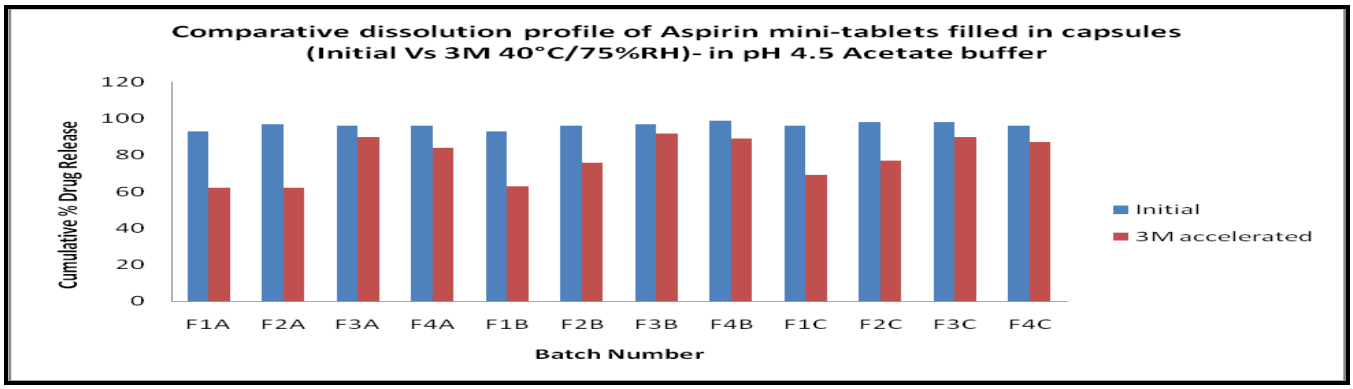

Figure 1: Comparative % drug release of Aspirin mini-tablets filled in capsules Initial Vs 3M 40/75 - in pH 4.5 Acetate buffer, for 30 minutes.

The assay, water content result indicates that batch number F1A, F2A, F1B and F2B are showing high degradation after 3M accelerated condition. Hence 4mg of alginic acid is not efficient to stabilize the formulation of aspirin mini-tablets. Formulation F1A, F2A, F1B, F2B, F1C and F2C are failing in dissolution after 3M accelerated condition. Hence 4 mg and 6 mg of alginic acid are not efficient to stabilize the formulation of aspirin mini-tablets. The formulations of F3A, F3B, F3C (with 8mg of alginic acid) and F4A, F4B and F4C (10mg of alginic acid) are showing assay, water by KF and dissolution within the specified limit after 3M accelerated condition. The formulation F3B is comparatively better and the drop in dissolution is not observed.

CONCLUSION

The preformulation result concludes that aspirin is highly unstable at alkaline condition and humidity, and degrades by hydrolysis. Aspirin is highly stable at the pH value of 3.7(pKa value of aspirin). A weak acid was evaluated from 4mg/unit to 10mg/unit. With the aid of weak acid 8mg per unit the product's pH was attained to pH 3.7, and the formulation was found to be stable at accelerated condition at 3month, and significant difference was not observed in comparison to initial. The formulation was evaluated with the moisture protective layer coating of 4% w/w to 8%w/w buildup. Whereas, the formulation with 6% w/w & 8% w/w moisture protective layer is found to be stable. Hence, the formulation with 8mg/unit of alginic acid and a moisture protective layer coating of 6% w/w was finalized as stable formulation.

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