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OPTIMIZATION AND EVALUATION OF ACRYLIC BASED POLYMER COATED DELAYED RELEASE ASPIRIN TABLET

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ABSTRACT

Background: Aspirin belongs to Non Steroidal Anti- inflammatory Drugs (NSAID) which is one the most commonly prescribed class of drug in order to alleviate pain fever and inflammation. Its pKa being 3.5 and physiochemical properties facilitate its absorption in the acidic media of stomach. But gastric irritation and ulcer causing property is the major undesirable characteristic. Delayed release tablet can be commercially as well as patient compliant option of the gastric irritant aspirin tablets. **Study** In order to resolve this issue the objective was to optimize a delayed release formulation by coating the core tablet with acrylic based polymers and compare their release, stability and manufacturability. Although different enteric coating polymers are available like polyvinyl acetate pthalate, cellulose acetate phthalate, hydroxyl propyl methyl cellulose (HPMC), but acrylic polymers were chosen for this study because of their better stability. Study involved drug excipient screening, core tablet formulation, screening enteric coating polymers for desired release profile. Drug excipient compatibility study was done first. Evaluation of granular aspirin was performed. Core tablets were then formulated and coated with Kollicoat MAE100P and Eudragit L100.Stability studies for one month was also performed. **Result & Conclusion:** The coating with Kollicoat MAE100P provided the better dissolution and free salicylic acid profiles as compared to coating with Eudragit L100. Thus coating of delayed release tablet with Kollicaoat MAE100P found to be more stable and fulfilled the objective.

KEYWORDS: Delayed release, Stability study, NSAID, Acrylates.

INTRODUCTION

NSAID (Non Steroidal Anti Inflammatory Drugs) is the most commonly prescribed class of drug in the modern medicine to alleviate pain fever and inflammation. Aspirin that is chemically acetyl salicylic acid belong to this class. In addition aspirin being acidic in nature, gastric irritation and ulceration are common side effects when taken empty stomach.

H.pylori and Aspirin are found to be associated with ulcer causing activity.[1,2]

On storage, aspirin releases salicylic acid in the form of free salicylic acid, which makes the aspirin tablets unstable along with increased weight and thickness, ultimately affecting the drug release properties. Aspirin unlike other weakly acidic drugs which are absorbed from stomach, does not follow normal absorption pattern across lipid membrane. Most of administered dose eventually gets absorbed from intestine. Based on physicochemical nature and pKa, the ideal condition for absorption of aspirin is within stomach. However, its absorption from intestine can be explained on the basis of enhanced solubility and stability in intestine.[3]

In the view of anticipated increased absorption due to enhanced dissolution, lesser degradation, no gastric irritation and better patient compliance, delayed release Aspirin have both clinical and commercial advantages. Developing stable, manufacturable enteric coated of aspirin requires selection of appropriate composition of ingredients including coating polymers for core and coated tablets.[4,5]

Different core and coating polymers were studied and analyzed in order to prepare enteric coated aspirin tablets in order to delay its release from stomach which included phthalates, acrylates, polyvinyl acetate phthalate.[6,7]

Hence the objective of this study was to screen different compositions for core tablets and coating composition for stable formulation. Study involved drug excipient screening, core tablet formulation, screening enteric coating polymers for desired release profile.[8-10]

MATERIALS AND METHODS

Material

Based on detailed study about different excipients which could be used to prepare a stable formulation, various excipients were selected as mentioned below.[11,12]

Aspirin granular was obtained from Alta laboratories as a gift sample. Citric acid was procured from Canton Laboratories pvt. Ltd. Maize starch, cross carmellose sodium, kollicoat MAE100 P and titanium dioxide were obtained from Signet Chemical Corporation. Microcrystalline cellulose PH102 & PH 112 were obtained from Brahmar cellulose pvt ltd. Starch 1500- LM was procured from Colorcon Asia Pvt. Ltd. Purified Talc was obtained from Lugenic Pharma and Stearic Acid was obtained from Signet chemical corporation, all other ingredients were of analytical grade.

Formulation development of core tablet of aspirin

Core tablets of aspirin were formulated using excipients which are suitable for direct compression.[13]

Details and composition are given in table 1.

Table 1: Formulation of different batches of Aspirin Core Tablet.

S.no.	Ingredients	F1	F2	F3
		Qty(g) /batch	Qty(g) /batch	Qty(g) /batch
1	Aspirin granular	243	243	243
2	Maize starch dried	5.67	-	-
3	Crosscarmellose sodium	1.62	7.2	7.2
4	Microcrystalline cellulose PH102	12.879	-	-
5	Colloidal silicon dioxide	2.43	3.6	3.6
6	Stearic acid powder	1.62	1.2	1.2
7	Citric acid	.081		-
8	Microcrystalline cellulose PH112	-	12	12
9	Starch 1500 LM	-	6	6

Preparation of aspirin core tablets

All tablets of Aspirin as per the composition mentioned in table 1 were prepared using direct compression process, wherein Aspirin was passed through 20 mesh sieve. All the excipients were also sifted through 30 mesh sieve. Initially aspirin, all excipients except stearic acid were loaded into Conta blender (Gansons). The powder was blended for 10 minutes further stearic acid was added and blended for 2 minutes. Blend was unloaded from blender,

compressed using rotary tablet 12 station compression machine (Rimek) with 6.35 mm round concave punches. Formulation 2nd and 3rd have same ingredients but the method of preparation was altered in 3rd formulation in order to enhance the drug dissolution. In trial 2 Aspirin granular was milled through multimill 2mm and then passed through #30. Oversized retained granules were milled through 1.5mm mulitmill and then passed through #30. Trial 3 was similar to trial 2except that in trial 3 aspirin was milled through multimill 2mm and the material was then passed through #40. Oversized retained granules were again milled through multimill 1.0mm and then passed through #40.

Preparation of seal coating solution of HPMC-6CPS

The solvents were taken in small stainless steel mixing vessel, were mixed using overhead stirrer at 500 RPM. The HPMC 6 cps was added to solvent mixture slowly and stirring was continued until a clear solution was formed. Tablets were loaded onto manual coating pan, warmed at 40^0C at pan revolutions for 10 minutes. Initial average weight of tablets was taken, HPMC solution was sprayed on bed of tablets maintained at 40˚C revolving in coating pan. The coating process was continued till 2% weight build up was achieved.

Table 2: Seal coating solution formula.

Ingredients	Trial 4	Trial 5
	Qty /tab in mg	Qty /tab in mg
HPMC-6cps	2	2
Isopropyl alcohol	21.12	21.12
Methylene chloride	31.68	31.68

Enteric coating of Core Tablets

The solvents were taken in small stainless steel mixing vessel, were mixed using overhead stirrer at 500 RPM. Excipients as per formula in table-3 were added to solvent mixture slowly and stirring was continued until nice uniform dispersion was formed. Tablets were loaded onto manual coating pan, warmed at 40^0C at pan revolutions for 10 minutes. Initial average weight of tablets was taken. Enteric coating solution was sprayed on bed of tablets maintained at 40˚C revolving in coating pan. The spray rate was maintained constant with pump RPM of 5. The coating process was continued till 8% weight build up was achieved.

Table 3: Enteric coating solution formula.

S. no.	Ingredients	Trial 4 (qty. gm/batch)	Trial 5 (qty. gm/batch)
1	Eudragit L100	19.665	-
2	Kollicoat MAE100P	-	19.665
3	Titanium dioxide	1.035	1.035
4	Purified talc	2.070	2.070
5	Yellow oxide of iron	0.33	0.33
6	Polyethylene glycol 6000	2.415	2.415
7	Iso propyl alcohol	64.17	128.34
8	Methylene dichloride	96.225	194.06

Drug-Excipient compatibility study

Table 4: Compatibility study at initial condition.

S.No	Name of drug/ Excipient	Ratio	Related Substance (Total impurity)	Moisture content	Appearance
1.	API	2 g.	Nil	Nil	White
2.	API + Maize Starch (dried)	1:1	0.03%	Nil	White
3.	API + Microcrystalline cellulose (pH -102)	1:1	Nil	0.07%	White
4.	API + Microcr ystalline Cellulose(pH-112)	1:1	Nil	Nil	White
5.	API + Starch (1500 LM)	1:1	Nil	Nil	White
6.	API+ Citric acid	1:1	Nil	Nil	White
7.	API + Cross carmellose sodium	1:1	Nil	Nil	White
8.	API+ Aerosil	1:1	Nil	Nil	White
9.	API + Stearic acid	1:1	0.06%	Nil	White
10.	API+ Eudragit L100	1:1	Nil	Nil	White
11.	API+ Kollicoat MAE100P	1:1	Nil	Nil	White
12.	API+HPMC-6cps	1:1	0.04%	0.08%	White
13.	API+ Talc	1:1	0.02%	Nil	White
14.	API+ Yellow oxide of iron	1:1	0.01%	Nil	White – yellow
15.	API+ Titanium dioxide	1:1	0.03%	0.02%	White
16.	API+ Instacoat ISE	1:1	Nil	Nil	White

Table 5: Compatibility study at 40ºC/75% RH.

S.No	Name of drug/ Excipient	Ratio	Related substance (Total impurity)	Moisture content	Appearance
1.	API	2 g.	Nil	0.02%	White
2.	API + Maize starch (dried)	1:1	0.08%	Nil	White
3.	API + Microcr ystalline cellulose (pH -102)	1:1	Nil	0.09%	White
4.	API + Microcr ystalline cellulose(pH-112)	1:1	Nil	Nil	White
5.	API + Starch (1500 LM)	1:1	Nil	Nil	White
6.	API+ Citric acid	1:1	0.01%	0.05%	White

7.	API + Cross carmellose sodium	1:1	Nil	0.05%	White
8.	API+ Aerosil	1:1	Nil	Nil	White
9.	API + Stearic acid	1:1	0.06%	Nil	White
11.	API+ Kollicoat MAE100P	1:1	0.03%	0.01%	White
12.	API+HPMC-6cps	1:1	0.08%	0.1%	White
13.	API+ Talc	1:1	0.06%	0.04%	White
14.	API+ Yellow oxide of iron	1:1	0.05%	0.03%	White – yellow
15.	API+ Titanium dioxide	1:1	0.16%	0.31%	White
16.	API+ Instacoat ISE	1:1	0.08%	0.04%	White

Where, API= Active pharmaceutical ingredient, RS= Related substances, MC=Moisture content,

A= Appearance, RH=Relative humidity

Evaluation of aspirin granule properties

Bulk density, tapped density, Hausner ratio & Carr's index of granules was evaluated by tap density apparatus. The tester was run at a rate of 300 taps/min for a total of 500 taps Initial volume of granules was measured. The granules were then placed in tapped density apparatus until the difference in the volume after consecutive tapping was less than 2%. For particle size analysis sieve #20, 40 and 100 were stacked one over another and mechanically set for vibration for about 5min. Fraction retained on each sieve was then calculated.

Evaluation of tablets

Weigh individually 20 units of tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage given in the USP pharmacopeia and none deviates by more than twice that percentage.

Hardness and Disintegration

Tablet hardness was determined using a Monsanto hardness tester and disintegration was determined using an automated programmable disintegration tester (ED-2L, Electrolab, Mumbai, India).

Friability

Tablet friability test was determined using USP friabilator (Electrolab EF-2). Tablets were subjected to 100 revolutions for 4 minutes. Percentage loss was calculated after weighing tablets before and after revolutions.

Thickness and diameter

Thickness and diameter of prepared tablets were tested by digital Vernier's caliper and the average from three readings was calculated.

DISSOLUTION

The dissolution profile of aspirin delayed release tablet formulation was evaluated using USP apparatus II (Paddles) with 900 mL of dissolution media. Paddle RPM was maintained at 100 with bath temperature of 37 ± 0.5 °C using electro-lab dissolution apparatus. The variation in the PH of GIT was mimicked by 2 hour dissolution study in 0.1N HCl and a sample was withdrawn after 2 hours and analyzed, whereas in pH 6.8 phosphate buffer the study was carried out for 1 hour 30 minutes, the aliquots were withdrawn at 15, 30, 45, 60 and 90 min these were filtered and estimated using UV/VIS spectrophotometer.[14]

Assay

Assay was determined in accordance with the USP 30/NF 25 monograph for aspirin delayed release tablets. The 20 tablets were crushed in mortar with pestle and triturated to get fine powder. The powder equivalent to 100 mg was taken in 20 mL volumetric flask, diluent (1% Formic acid in Acetonitrile) was added to mark and sonicated for 10 minutes with intermittent shaking. The solution was centrifuged at 500 RPM for 10 minutes. Supernatant (1 mL) was taken into 10 mL volumetric flask and volume was made up to mark with diluent. The standard solution (0.5 mg/mL) was prepared in diluent. The sample and standard solutions were analyzed by using liquid chromatography using column ODS C18 column 4.0 X 300 mm, 10µ. The quantification was done at 280 nm detector. Mobile phase was a mixture of sodium 1-heptane sulfonate 2g, acetonitrile 150 mL and water 850 mL with pH adjusted to 3.4 pumped at flow rate of 2 ml/minute.[14]

Assay of free Salicylic Acid

The method for assay of Salicylic acid is same as Aspirin method. Salicylic acid is eluted earlier than Aspirin.[14]

RESULTS AND DISCUSSION

Granular properties

The granular properties of selected blend (Formulation-3) is given in table-6. The granular properties indicated excellent flow for granules. The percentage of fines was <40%. The bulk density, tapped density, Hausner's ratio and Car's index were within acceptable limits.

Physical properties of core tablets

Thickness was between was between 2.7 to 2.8mm, hardness close to 5kg, and friability was less than 0.1%. Hence all parameter were meeting general requirement of core tablets to be coated.

Formulation of core tablets

The primary objective of this study was to prepare a delayed release formulation by comparative evaluation of two acrylic polymers for stability, drug release and manufacturability of the dosage forms. Although different enteric coating polymers are available like polyvinyl acetate pthalate, cellulose acetate phthalate, HPMC, but acrylic polymers were chosen for this study because of their better stability.

The Cellulose acetate phthalate films used are hygroscopic and dissolve only above pH 6, which in turn delays drug absorption. HPMC as enteric polymers are quiet stable compared to Cellulose acetate phthalate films, they dissolve at pH 5 to 5.5, but are comparatively costly. In contrast Acrylate polymers are non-toxic, they offer high solid content with low viscosity and due to micronized form of polymers requires less quantity to attain perfect coating, further since no phthalate is present, acrylates offer better stability.[15]

A stable core tablet with better dissolution profile was prepared using starch LM which have low moisture profile with better dissolution property and microcrystalline cellulose MCC pH 112 was used, dissolution of about 85.45% was achieved from this formulation. Further keeping all the variations constant only the method was modified in formulation 3rd of core tablets, for optimization wherein the particle size of the aspirin API was reduced by passing it through a mesh of size #30 thus resulting in dissolution of about 90.8%.

Coating of the optimized 3rd formulation core tablet was done using eudragit L100 and kollicoat MAE100P.

Granule properties of aspirin granular were measured as per USP and found within the limits. Hence it was found that the flow of powder was excellent.

Table 6: Granular properties of aspirin.

Granule Properties	Result
Bulk density	0.69g/ml
Tapped density	0.77g/ml
Hausner ratio	1.11
Carr's index	9.90%
% retained on sieve 20	7.12%
% retained on sieve 40	69.25%
1% retained on sieve 100	98.25%

Table 7: Results for Aspirin core tablet.

Formulation	Parameters							
	Weight (Mg)	Thickness (mm)	Diameter (mm)	Hardness (Kg)	Friability (%W/w)	Disintegration time (Minutes-Sec)	Dissolution (%)	Assay (%)
F1	81.13	2.77	6.35	4.8	0.05	12min 5sec	78.83	97.12
F2	91.3	2.8	6.32	5	0.07	1min 2 sec	85.45	97.0
F3	91	2.79	6.3	5	0.08	55sec	90.8	98.6

Table 8: Evaluation studies of Coated Aspirin Tablets using Eudragit L100 & Kollicoat MAE100P as Coating Polymers,

Formulation	Avg. weight	Thickness	Diameter	Assay	FSA	Dissolution
F4	100.8	2.99	6.39	102.52	0.01	In acid phase 8.65 In buffer phase 93.83
F5	101.1	2.94	6.40	100.66	0.18	In acid phase 2.98 In buffer phase 96.57

The enteric coated tablets were further kept for one month long term and accelerated study and passed in all the evaluation parameters. Hence a stable formulation was prepared which was further kept for stability studies.

One month stability results of 5th trial

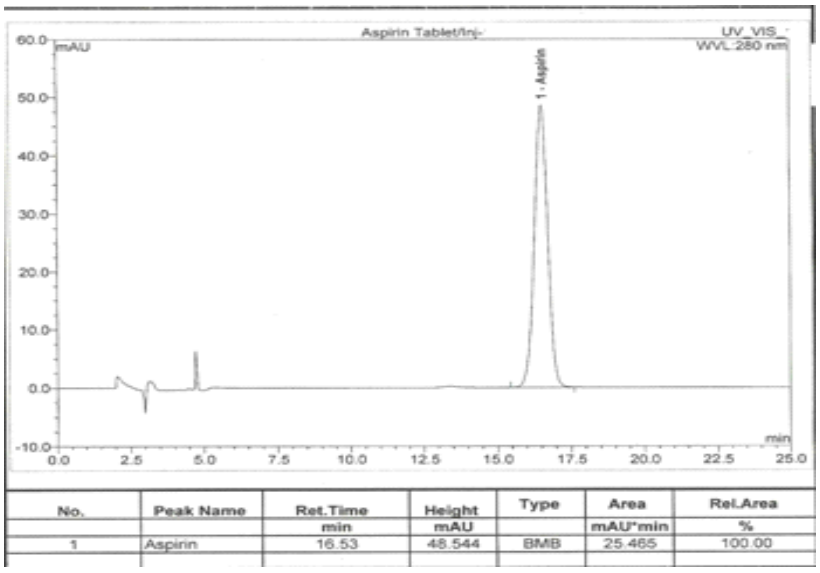
Appearance: Yellow colored round shaped, coated, biconvex tablets, plain on both sides.

Table 9: One month stability results.

Trial 5th		Coated tablet evaluation		
Parameters	Specification	Observation		
		Initial	1 Month stability report	
			30°c/65% RH	40°c/75% RH
Assay	95-105%	102.66%	101.82%	99.45%
FSA	NMT 3%	0.18%	0.40%	1.34%
Dissolution-				
In acid phase	NMT 10%	2.98%	4.67%	7.19%
In buffer phase	NLT 80%	96.57%	94.12%	90.09%

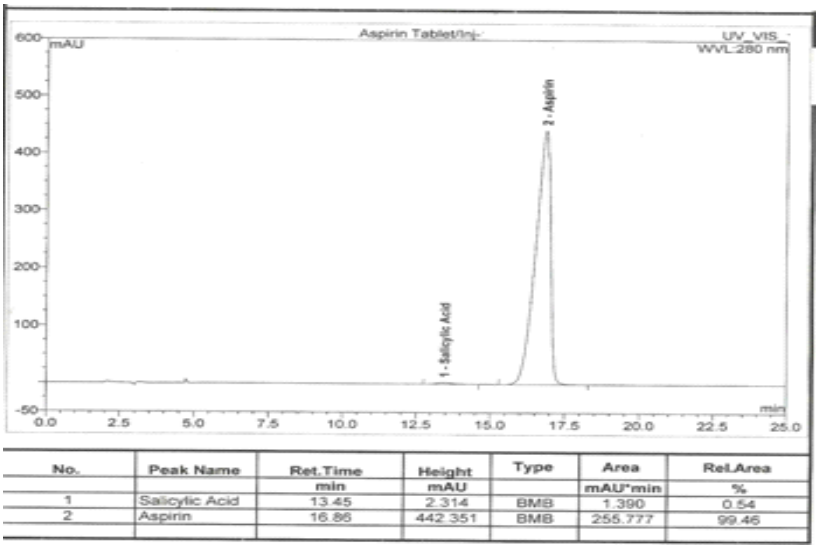
Average weight	101.0±2%	101.1	101.9	102.8
Thickness	3.0±0.2	2.94	3.05	3.18
Diameter	6.4±0.2	6.4	6.49	6.51
Disintegration				
In acid phase	**Nil (upto 1 hr)**	**nil**	**nil**	**nil**
In buffer phase	Disintegrate completely within two hours	45min.	49min.	59min.
Uniformity of weight	Avg.weight ±10%	-3.01%,+1.87%	-6.3%,+4.2%	-1.4%,+1.6%

All the physical and chemical parameters were found within the limits after one month stability testing. Hence the formulation was considered further for three and six months stability studies.



No.	Peak Name	Ret.Time	Height	Type	Area	Rel.Area
		min	mAU		mAU*min	%
1	Aspirin	16.53	48.544	BMB	25.465	100.00

Figure 1: Assay of aspirin tablet.



No.	Peak Name	Ret.Time	Height	Type	Area	Rel.Area
		min	mAU		mAU*min	%
1	Salicylic Acid	13.45	2.314	BMB	1.390	0.54
2	Aspirin	16.86	442.351	BMB	255.777	99.46

Figure 2: Graph for (free salicylic acid) FSA of aspirin tablet.

CONCLUSION

A low dose aspirin formulation for the treatment of pain, fever, inflammation and cardiovascular diseases was prepared. Since aspirin carries high risk of gastric upset and ulceration it was enteric coated to prevent its release in the stomach and effect its release in the intestine.

While formulating the core tablet trial first did not pass the evaluation parameters as per monograph. Trial second passed in all the evaluation parameters but in order to enhance the bioavailability of core tablet one more trial was taken using same ingredients as in trial second but different process was applied for its method of preparation. Further enteric coating was evaluated on trial third using different acrylic polymers.

The coating with kollicoat MAE100P provided the better dissolution and free salicylic acid profiles as compared to coating with eudragit L100. It also passed in one month stability studies. Hence it was concluded that both polymers, eudragit L100 and kollicoat MAE100P provided the necessary physical and chemical properties to the moisture sensitive drug. But due to its higher molecular weight better coating was achieved using kollicoat MAE100P along with optimum results. Thus kollicoat MAE100P was preferred over eudragit L 100.

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