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Formulation and evaluation of oral dissolving film of aspirin: A Novel Approach

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ABSTRACT

Aspirin belongs to the nonsteroidal anti-inflammatory drug class used to reduce pain, fever, or inflammation. it additionally has an antiplatelet effect by inhibiting the COX1 activity in the platelet to prevent the manufacturing of thromboxane A2, which acts to bind platelets together throughout coagulation in addition to causing vasoconstriction and bronchoconstriction. Present work focuses only on the anti-platelet activity of Aspirin. The work aims to design, develop and evaluate an oral film containing Aspirin (using a dose of 37.5 mg) to increase the bioavailability of the drug and avoid extensive metabolism. Films were prepared by solvent casting method using excipients like film-forming agent (HPMC E5, HPMC E15, PVA, PVP K30), plasticizer (PEG 400, Glycerol, Propylene Glycol), Super disintegrant (Crospovidone, Croscarmellose and Sodium starch Glycolate) and sweetener (Aspartame). Formulated preliminary batches were subjected to characterisation such as the thickness of the film, folding endurance, and disintegration time. Sublingual films containing HPMC E15 LV Premium (film-forming agent), PEG 400 (plasticizer) and CCS (Super disintegrant) show good results as that of marketed film formulation. Optimized batches were prepared among which batch B1, batch B3 and B5 showed desired drug release 95.93%, 89.151% and 90.21% respectively with 30, 32 and 37 seconds disintegration times.

KEYWORDS: Oral dissolving film, Aspirin, Solvent casting method, Anti-inflammatory, Antiplatelet effect.

INTRODUCTION:

Oral dissolving film is a solid dosage form that quickly dissolves in the oral cavity, forming a solution or suspension without requiring the administration of water. In the late 1970s, oral dissolving film drug delivery systems were created as a substitute for tablets, capsules, and syrup for elderly and paediatrics patients who have trouble swallowing typical oral dosage forms,

which are based on transdermal patch technology(1)(2)(3). Right now fifteen companies are involved in the manufacturing of film (1). It is an innovative approach to drug administration, its edible dosage forms and the API are supposed to pass through the oral mucosa and there is no extra water needed to apply the dosage form so it is pretty convenient for the patients and therefore ideal for patients with difficulties swallowing. Lingually applied thin film should disintegrate pretty fast within seconds. Very often lingually applied thin films are bioequivalent to immediate-release tablets and show fast onset of action.. Buccal film is more AUC-focused and especially if there are any side caused by the high Cmax of the drug this can be somehow reduced by using buccal fast dissolving film(4). The condition known as atherosclerosis can cause plaques inside arteries to burst. The plaque's substance encourages platelets to adhere to the plaque right away, which leads to the formation of blood clots inside the artery. Blood flow to the heart muscle inside a coronary artery is stopped beyond the point of occlusion. If the blockage is in a major artery, this can frequently result in a cardiac arrest(5).

Acetyl derivative of salicylic acid is acetylsalicylic acid, also marketed under the trade name Aspirin. It provides relief from aches in the muscles and joints as well as headaches. Aspirin has been used to treat rheumatoid arthritis, rheumatoid fever, and minor infections because it is also effective in lowering fever, inflammation, and swelling(6).

Rationale Behind the Work

Compared to conventional dosage forms, oral mucosal administration methods have advantages including longer residence times and simpler application. These dose forms are practical for busy persons without access to water, the elderly, the disabled, and travellers. The formulation should dissolve quickly because there isn't much saliva in the buccal and sublingual areas. This method has been used to give a variety of BCS class II medications. Since aspirin is a non-steroidal anti-inflammatory medicine (NSAID), it is often prescribed to treat rheumatoid arthritis, fever, and cardiovascular issues. The medicine in question is an ester-based formulation that is just barely soluble in water(7). For these medications, it is necessary to produce formulations with the least amount of water possible for buccal administration in order to maximize stability and enhance the distribution of the medication at the site of buccal absorption. Typically, older adults need more prescription drugs since they often have several health issues, such as dysphagia. this happens when the physiology of swallowing alters with age because of a decrease in the

suppleness of connective tissue and muscular mass, which causes a loss of strength and motion(8). Even lower doses of aspirin are gradually becoming recognized as a cause of gastrointestinal bleeding. Endoscopically normal gastric mucosa, asymptomatic and symptomatic lesions such as erosion and ulcer, and consequences of an ulcer include bleeding and perforation this is dose-dependent(9). Most oral aspirin dosages enter the systematic circulation between 50 and 70 percent of the time; the remaining portion is inactivated by the liver and plasma by carboxyl esterase (first pass effect)(10)

All these problems can be overcome using the sublingual film of aspirin as it directly passes the gastrointestinal tract, and liver and there is no need to swallow the drug so convenient for patients with dysphagia (11).

Noticeable advantages of oral dissolving films are as listed below (1)(2)(12)

- Tailored absorption kinetics
- Fast onset of action possible
- Improved bioavailability
- Avoid side effects due to high Cmax
- Avoids hepatic first-pass metabolism effects
- Reduces variability for drugs with food effect
- Improved compliance
- Application in pediatrics and geriatric population
- Enhanced stability
- Easy to handle and administration
- The film is small enough to fit in a patient's wallet and pocket.
- The film is simple to make and helps to mask bad tastes.
- Ease Transportation.

Mouth-dissolving film has also a clear advantage over the oral dissolving tablets (ODT) (12)(13)

- ODT can occasionally be fragile and challenging to handle, store, and carry.
- A lot of ODTs are made via the costly lyophilization process.
- ODT has a fear of choking.

- Fast-dissolving tablet has lesser dissolution due to less surface area.

Some of the disadvantages are also there of oral dissolving film as mentioned below:

- This dosage form is not permitted to be used in a high dose range.
- Since most medications have an unpleasant taste, taste masking is necessary.
- Because oral films are delicate, they need to be packaged carefully.
- One major obstacle is achieving dose consistency.
- Oral films are susceptible to moisture.
- Unsuitable for dose forms with prolonged release.
- This kind of administration makes it difficult to eat, drink, or converse.
- Drugs that irritate oral mucosa are not a suitable candidate.
- Oral films should have high oral bioavailability.

MATERIALS AND METHODS:

Hydroxypropyl methylcellulose E15 LV Premium USP (14) is used as a film-forming agent, Polyethylene glycol(15) is used as a plasticizer, Croscarmellose sodium(15) used as a super disintegrate and Aspartame(15) as a sweetening agent. API and all the materials used in the study were procured from the supplier from Ahmedabad.

METHOD OF PREPARATION (16)(2)

Aspirin-containing oral dissolving film was made by solvent casting method. Aspirin and HPMC E15LV were added to ethanol to prepare solution 1. All the other ingredients like sodium starch glycolate, aspartame, flavouring agent, and colouring agent were dissolved in water to prepare solution 2. Both the solutions were mixed and kept for sonication to obtain a homogenous mixture. The prepared mixture was casted on to a Petri dish and kept for a side for 10 minutes for stabilization. After that petri dish was kept in hot air oven for drying at 40-45^{0}C. after proper drying, the film was peeled out from the petri dish and stored in air air-tight plastic bag till further use.

Before the finalization of the excipients to be used in the formulation, the screening of the various excipients was done as below.

Screening of Excipients(17)(18)

Selection of suitable solvent

Different solvents were used for the solubility study. For example, distilled water, methanol, ethyl alcohol (95%), dimethyl sulfoxide (DMSO). Based on the solubility of aspirin in different solvents ethyl alcohol (95%) was selected as it has shown maximum solubility.

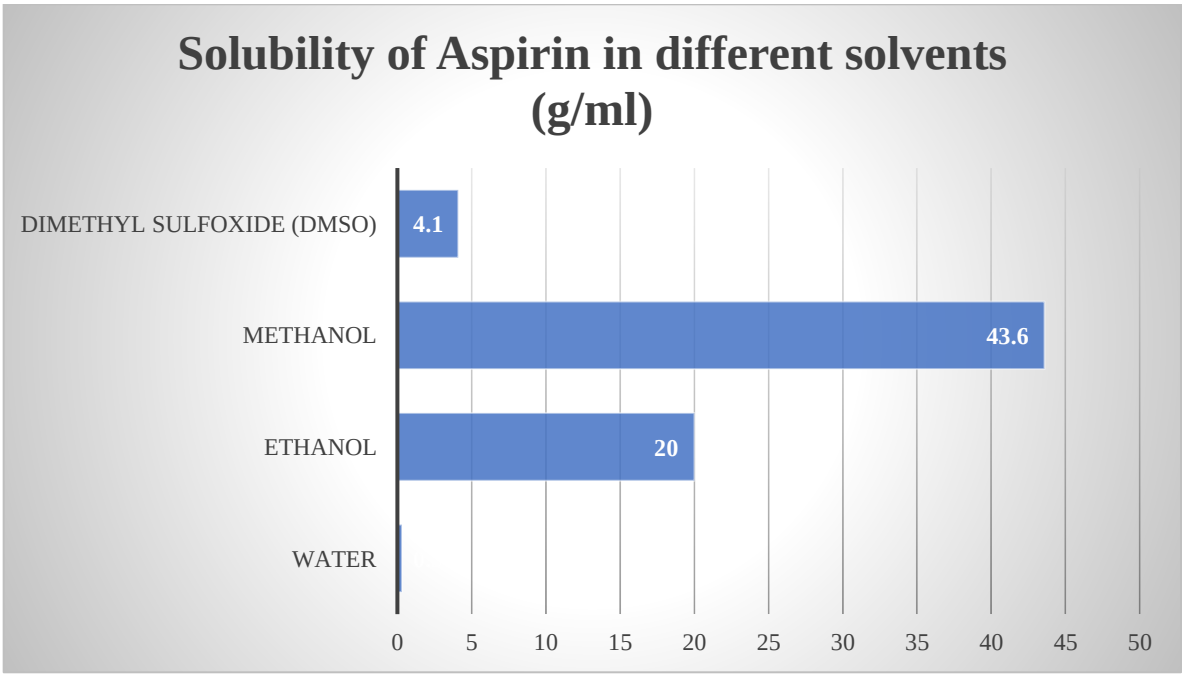

Figure 1. Solubility study

Screening of film forming agent(18)(19)

For the selection of the best film-forming agent film was prepared by using different film-forming agents like HPMC E5, HPMC E15, PVPK90 and HPMC E15 LV PREMIUM. The film was prepared by taking various concentrations (40%, 45%, 50%) of each film-forming agent and by keeping all the other ingredient quantities fixed. The prepared film was evaluated for stickiness, folding endurance, disintegration time, thickness and clarity of the film.

From the different prepared films HPMC E15 LV Premium: Showed satisfactory results on drying, less disintegration time, good elasticity, and Easy to peel off. While film prepared by using HPMC E5 has shown stickiness, Film prepared by HPMC E15 have shown more disintegration time, film prepared by PVP K30 not dried. So HPMC E15 LV Premium is selected for further study.

Screening of Plasticizer(20)

Different plasticizer like Polyethylene glycol 400, glycerol & propylene glycol were taken in different proportion (35%, 25%, 10% and 5%). The prepared film was evaluated for stickiness and folding endurance.

From the different prepared films, film prepared with PEG 400 have shown good results as compared to other plasticizers. It has shown less disintegration time, non-stickiness and good elasticity. While film prepared with glycerol was sticky and hard to peel off. Film prepared with propylene glycol was shrunken on drying. So PEG 400 was selected for further study.

Selection of Super disintegrants

Two different super disintegrant sodium starch glycolate and cross-carmellose sodium were taken to prepare the film. The prepared film was evaluated for stickiness and disintegration time.

The film prepared with sodium starch glycolate was moderately sticky and have taken more time to disintegrate. While film prepared with cross caramellose sodium was non-sticky and showed less disintegration time. So it was selected for further study.

Selection of Solvents concentration (Ethanol)

Film was prepared by taking various concentrations of ethanol (95%v/v, 75%v/v and 60% v/v). the prepared film was evaluated for stickiness and clarity.

Film prepared by using 75% v/v ethanol shows good solubility of API as well as other ingredients as compared to other concentrations of ethanol. So it was selected for further study.

Composition of the final batch after screening of excipients

Ingredients(g)	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**
Aspirin (g)	1.66	1.66	1.66	1.66	1.66	1.66	1.66	1.66	1.66

HPMC LV Premium(g)	0.5	0.5	0.5	1	1	1	1.5	1.5	1.5
PEG400(ml)	0.5	1	1.5	0.5	1	1.5	0.5	1	1.5
Croscarmellose sodium(g)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Aspartame (g)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Sodium Bicarbonate(g)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Flavour (Lemon syrup) (ml)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Colour (Sunset Yellow)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Ethanol (75%v/v)	20	20	20	20	20	20	20	20	20

Table1: Final batch composition

Characterization of prepared oral dissolving films:

Thickness of film

The thickness of the prepared oral dissolving films was measured by using a micrometre screw gauge (Mitutoyo)(7) (21)(22).

Folding Endurance

It is determined by repetitive folding of the strip at the same place till the strip breaks down.

Surface pH

The surface pH plays an important role in determining possible side effects due to changes in pH in vivo. If the film is having acidic or alkaline nature then it may cause irritation of the mucous membrane. The physiologic pH of the oral fluids is between 6.0 and 7.5(23) For the measurement of pH the prepared film was placed in a petri dish and it was moistened with 0.5 ml of distilled water and kept for approximately 1 hour. The electrode of the pH meter was kept in contact with the surface of the film and allowed for equilibrium for 1 minute. The average of the three readings is shown in the result(24) (25).

Disintegration time

Disintegration time was measured by manual method. The film was taken in a beaker containing 25 ml of distilled water. Stirring was provided every 10 sec. when the film totally get broken that time was noted down as a disintegration time as shown in result.

Weight variation

This test is performed by taking 10 films of the same batch & weighing it. After that, average weight is taken. After calculating the average weight, individually calculated the % weight of film.

$$\text{Weight variation} = \frac{\text{Weight of individual strip}}{\text{Average weight of strip}} \times 100$$

Content uniformity

Content uniformity should be in between the range of 85 – 105% as per label claim. Drug content was determined by dissolving the film in 100 ml distilled water. An aliquot of 1 ml sample was withdrawn and diluted further as required. After passing the solution through Whatman filter paper, it was measured at 227 nm using a UV spectrophotometer against a blank made using fake film that had undergone the same treatment. For every batch of the film, content uniformity studies were conducted in triplicate. content uniformity of the film should be within the range 85-115%.

Moisture content

Moisture content is measured by placing the film in a hot air oven & at 20 min intervals the weight of the film is measured till it gives constant weight**.**

$$\%\ \text{Moisture content} = \frac{\text{Initial weight of film} - \text{Final dried weight of film}}{\text{Initial weight of film}} \times 100$$

In vitro dissolution study

An in-vitro dissolution study was carried out by using a USP type I apparatus. The specific-sized film containing a unit amount of dosage was placed in USP apparatus 1 and further placed in 300 ml freshly prepared dissolution medium maintained at 37+/- 0.5 ^{0}C and rotated at 100 rpm. A quantity equivalent to 5ml of sample was withdrawn at various time intervals (0,5,10,15,20,25 min) the same amount of buffer was replaced after each time interval. the solution was filtered using Whatman filter paper and analyzed spectrophotometrically at λ_{max} 227 nm.

Result and Discussion

Batch No	Thickness of the film (mm)	Folding endurance	pH	Disintegration time (Sec)
B1	0.359	101	7	30
B2	0.250	155	6.81	56
B3	0.299	60	7.02	32
B4	0.435	128	6.95	50
B5	0.248	141	6.79	37
B6	0.404	137	6.93	41
B7	0.369	196	6.58	74
B8	0.455	306	6.67	57
B9	0.325	252	6.92	64

Table 2: Result of Thickness, Folding endurance, pH, Disintegration time

From the above table following conclusion can be made, batch B2 & B5 shown least thickness value, batch B1, B4, B5 & B6 have shown satisfactory folding endurance results, all the batches have shown pH within the range and batch B1, B3 and B5 have shown less disintegration time.

Weight variation

Weight variation test results of 10 film of same batch, the result of the test found satisfactory.

B1	B2	B3	B4	B5	B6	B7	B8	B9
102.598	98.0946	106.695	96.5406	106.264	95.7684	91.6667	108.182	91.2256
99.9334	100.212	100.418	106.195	100.671	90.5716	98.3333	101.818	97.493
102.598	100.212	108.787	106.999	93.9597	85.3749	99.1667	100	98.1894
91.9387	100.917	92.0502	97.3451	100.671	100.223	95.8333	99.0909	94.7075
102.598	107.269	80.5439	98.9541	86.1298	96.5108	100	100	108.635
97.9347	97.3888	103.556	95.7361	102.908	89.0869	102.5	99.0909	103.064
102.598	107.269	99.3724	104.586	101.79	97.9955	102.5	95.4545	102.368
99.2672	96.6831	105.649	91.7136	100.671	95.7684	112.5	102.727	105.153
100.6	96.6831	97.2803	102.977	104.027	88.3445	99.1667	100	96.7967
99.9334	95.2717	105.649	98.9541	102.908	160.356	98.3333	93.6364	102.368

Table 3: Weight variation test results

Drug content & Moisture content

Batch No	Drug content (%)	Moisture content(%)
B1	83.13359	6.122449
B2	97.55642	4.854369
B3	88.73671	10.52632
B4	112.1868	8.849558
B5	91.84955	4.255319
B6	70.37095	4.347826
B7	80.74708	6.504065
B8	90.18936	8.108108
B9	89.15175	5.982906

Table 4: Drug content and Moisture content results

From the above table, Batch no B2, B3, B5, B8 and B8 have shown drug content within the range. The moisture content in an ideal buccal film should be <5%. From the above table, Batch no B2, B5, B6 have shown moisture content within the range.

In vitro dissolution study

Time (min)	% CDR								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
0	0	0	0	0	0	0	0	0	0
1	10.176	6.287	39.9	8.778	11.42	16.48	13.6	11.28	12.32
2	51.66	19.727	60	36.23	35.67	40.352	35.104	31.2	30.12
3	95.93	42.15	89.151	68.66	90.21	77.072	75.63	75.77	85.584

Table 5: In-vitro dissolution study data

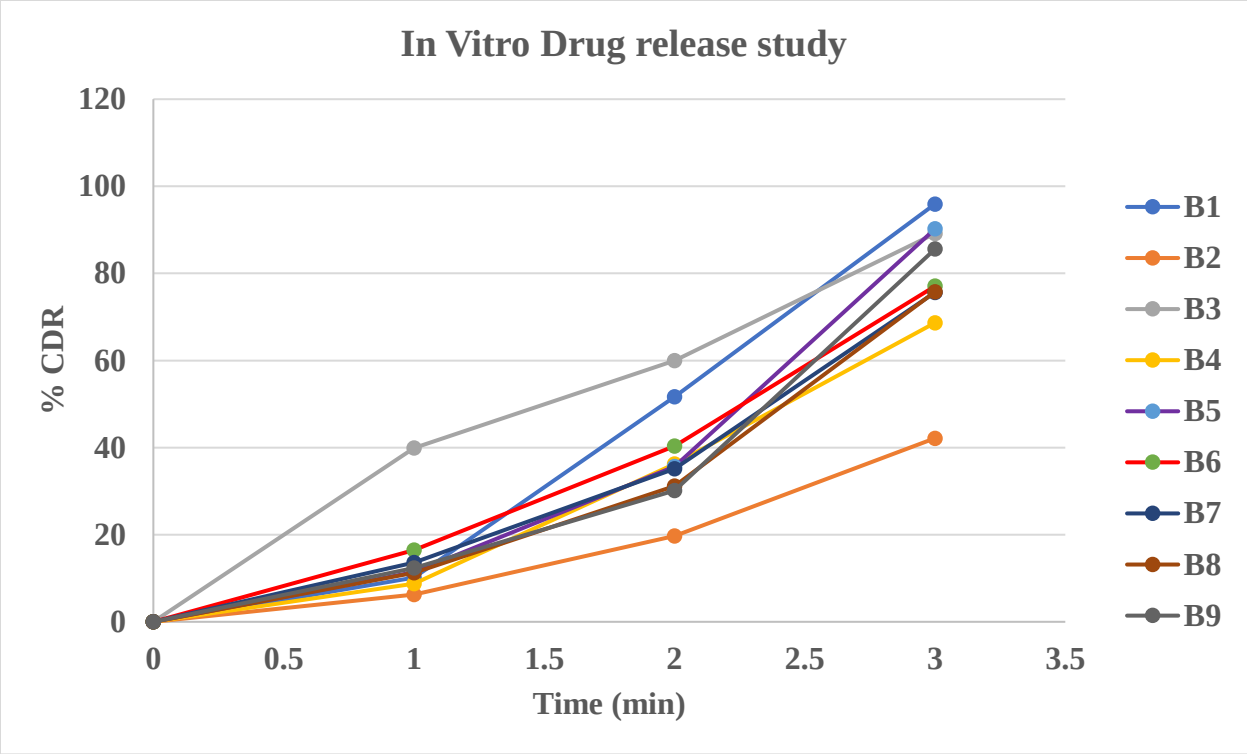

Figure 2. In Vitro Drug release study

Among 9 batches batch B1, batch B3 and B5 showed desired drug release 95.93%, 89.151% and 90.21% respectively

Summary and conclusion

Aspirin has antiplatelet effect by inhibiting the COX1 activity in the platelet to prevent the manufacturing of thromboxane A2, which acts to bind platelets together throughout coagulation in addition to causing vasoconstriction and bronchoconstriction. Objective of the work is to design, develop and evaluate films containing Aspirin (using dose 37.5 mg) to increase the bioavailability of drug and avoid extensive metabolism. Solvent casting method is selected to prepare a film as this method requires less time and cost effective among other oral film making techniques. Preliminary batches of film were prepared using different film forming agents such as HPMC E5, HPMC E15, HPMC E15 LV Premium, PVA and PVP K30 at different concentration; plasticizers such as PEG 400, Glycerol and Propylene Glycol; and Super disintegrants such as Cp, CCS and SSG. Prepared preliminary batches were evaluated by parameters such as thickness of film, disintegration time and folding endurance. Polymers gives desired results were subjected to further study. Sublingual films containing HPMC E15 LV

Premium (film forming agent), PEG 400 (plasticizer) and CCS (Superdisintegrant) shows good result as that of marketed film formulation. Weight variation, Content uniformity, Moisture content and In-vitro drug release tests are performed on the optimized batches. Among 9 batches batch B1, batch B3 and batch B5 showed desired drug release 95.93%, 89.151% and 90.21% respectively with 30, 32 and 37 seconds disintegration time. Further it is concluded that batch B5 is found to be the finalized batch with the drug release 90.21% at the end of 3 min, disintegration time of 37 secs and having folding endurance 141.

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