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FORMULATION AND EVALUATION OF METFORMIN FAST DISSOLVING FILM BY SOLVENT CASTING METHOD

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ABSTRACT
Metformin is indicated as an adjunct to diet and exercise to increase glycaemic control in adults and paediatric patients 10 years of age and older diagnosed with type 2 diabetes mellitus (DM). The present study is deal with formulation, optimization and evaluation of Metformin mouth dissolving films. Type 2 diabetes mellitus is the condition where instance effect of drug is required. Metformin is one of the most popular drug which used in the treatment of DM. The mouth dissolving films was prepared by using solvent casting method. The concentration of citric acid, sucrose, glycerin and Sodium starch glycolate were kept constant in all formulations (F1-F9) and varying concentration of hydroxy propyl methyl cellulose (HPMC-E15) and methyl cellulose. All the formulations were evaluated for appearance, shape, thickness, weight uniformity, folding endurance, percent elongation, tensile strength, drug content, disintegration time, in-vitro dissolution studies. The formulation 'F3' was found to be optimized formulation. It shows results for all evaluation parameters such as weight variation 68.2 mg, folding endurance 13, drug content 99.87%, percent elongation 11, disintegration time 20 sec, and in-vitro dissolution study 82 % at the end of 5 min.

KEYWORDS: Fast dissolving film, Metformin, HPMC-E15, Methyl cellulose, Diabetes mellitus.

INTRODUCTION
Oral route has been one of the most popular commonly employed routes of drug delivery due to its ease of administration, pain avoidance, patient compliance, least sterility constraints, flexible design of dosage forms and cost effectiveness to manufacturing process and versatility (to accommodate various types of drug candidates). Approximately one-third part of the population, mostly the geriatric and pediatric patients has a problem of swallowing it leads to reason poor patient compliance with oral tablets/capsules drug treatment which minimizes the therapy effectiveness. Tablets are most general oral formulations available in worldwide market and preferred by both patients and physicians. Several novel technologies for oral delivery have recently available to handle the physicochemical and pharmacokinetic appearances of medicine, while improving patient complianc.[2,6]

Fast dissolving drug delivery structure were first developed within the late 1970s as an alternate to tablets, capsules, and syrups for paediatric and geriatric patients who experience problems in swallowing traditional oral solid dosage forms. The new technology of fast dispersing dosage forms is thought as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and perception of of these dosage forms are similar.[1,7]

A solid dosage form that dissolves or disintegrates quickly within the oral fissure, leading to solution without the necessity for the administration of the water, is thought as an oral fast-dispersing dosage form. Difficulty in swallowing (dysphagia) is common among all the age groups, especially in elderly, and is additionally seen in swallowing conventional tablets and capsules. Dysphagia is related to many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck thyroid therapy, and other neurological disorders, including brain disorder. the foremost common complaint was tablet size, followed by surface, form and taste. the matter of swallowing tablet was more evident in geriatric and pediatric patients, further as travelling patients who might not have ready access to water. [4,16]

Criteria for fast dissolving film[2,18]
Fast dissolving film should: -

- ❖ No requirement of water to swallow, but it should dissolve or disintegrate in the mouth in period of seconds.
- ❖ Be compatible with taste masking.
- ❖ Have a pleasant mouth feel.

- Exhibit low sensitivity to environmental conditions such as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipment at low cost.
- Leave minimum or no residue in the mouth after oral administration.

Salient feature of fast dissolving drug delivery system[2,18, 19,21]

- Ease of administration for patients who are mentally ill disabled and uncooperative.
- Require no water.
- Overcomes unacceptable taste of the drugs.
- Can be designed to leave minimal or no residue in the mouth after administration and also provide a pleasant mouth feel.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Cost effective.

Need for fast dissolving drug delivery systems[1,24]

Fast dissolving drug delivery systems can improve acceptance and compliance in patients with dysphasia. Similarly, from market point of view, introduction of FDDDS will assist life cycle management of drug especially if the drug is patent protected.

MATERIAL AND METHOD

Material

Metformin and all other chemicals used were obtained from commercial sources and were of analytical grade.

Table no. 1: Formulation trial.

Sr. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Metformin	500	500	500	500	500	500	500	500	500
2.	HPMC E15	250	750	500	250	500	750	500	250	750
3.	Methyl Cellulose	200	600	400	400	200	400	600	600	200
4.	Citric Acid	20	20	20	20	20	20	20	20	20
5.	Sucrose	20	20	20	20	20	20	20	20	20
6.	Glycerin	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml
7.	SSG	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg
8.	Water	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml

Procedure

The water-soluble polymers and plasticizers were dissolved in distilled water. The solution is stirred up for 2 hrs. in the magnetic stirrer and kept aside to remove all air bubbles entrapped. Meanwhile, the excipients and drug were dissolved and stirred well for 30 min, after the completion of stirring both the solutions are mixed together. Finally, the solution is casted on a suitable petri-plate to form a film. The plates were kept in a hot air oven at 60° c for 1 hour. The dried film was gently separated from glass plate and cut into a desired size.[1,5]

Evaluation of Mouth Dissolving Film[3-15]

1. **Thickness:** A micrometer screw gauge was used to measure the film thickness. In order to obtain uniformity of film, thickness is measured at 5 different locations. The thickness of the film should be less than 5 %.

2. **Weight variation:** Ten films were randomly selected and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation.

3. **Folding Endurance:** To determine folding endurance, a film is cut and rapidly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Topical folding endurance for film was between 100-150.

4. **Percentage elongation**
   It was calculated by
   $$\text{Percentage elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

5. **Tensile Strength:** Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the formula,
   $$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{strip width}}$$

6. **In-Vitro disintegration:** Disintegrating time is defined as the time (sec) at which a film breaks when brought in contact with water or saliva.

Petri dish method

2 ml of distilled water was placed in the petri dish and one film was added on the surface of water and the time measured until the oral film was dissolved completely.

7. **In-Vitro dissolution:** 900 ml of o.1 N HCL was used as a media, at was maintained at 37+0.5 °c while the basket was set at 100 rpm. A film sample of 4 cm^2 (2×2 cm) was cut and taken into the basket. 5 ml of the sample were taken every 60 seconds and the same amount was replaced with fresh 0.1 N HCL. The withdrawn samples were filtered and analyzed using a UV spectrometer at a wavelength of 232 nm.

8. **Drug content:** This test was performed by dissolving a 4 cm^2 area of film in 50 ml of 0.1 N HCL with stirring. This solution was filtered using a whatmann's filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analyzed using UV spectrometer.

9. **Assay:** This test was performed by dissolving a 4 cm area of thin film in 50 ml of pH 6.8 phosphate buffer with stirring. This solution was filtered using a Whatmann's filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analyzed using UV spectrophotometer.

Preparation of calibration curve of metformin[22]

Weigh quantity of Metformin (100mg) place in 100 ml of standard volumetric flask and make up the volume with simulated saliva pH 6.8. The stock solution obtained is 1000 µg/ml solution. Aliquots of 0, 1, 2, 3, 4, 5, 6 ml of stock solution pipette out into 100 ml standard volumetric flasks and final volume adjust up to 100 ml with simulated saliva pH 6.8 to give the concentration of 5, 10, 15, 20, 25 and 30µg/ml. The absorbance measure at 234 nm in UV spectrophotometer against reagent blank with simulated saliva pH 6.8.

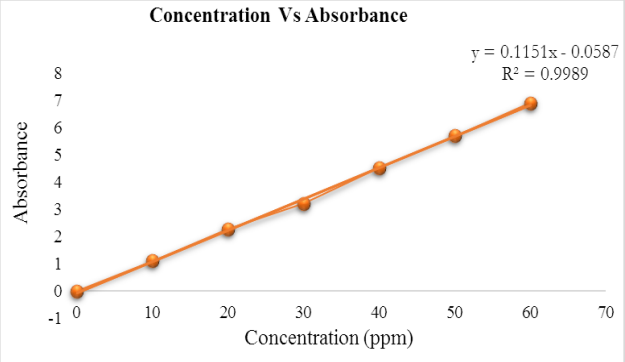

Fig no. 1: Standard calibration curve of metformin.

RESULT AND DISCUSSION

Table no. 2: API Characterization: Metformin.

Sr. No.	Test	Specification	Result
1.	Description	White crystalline powder	White crystalline powder
2.	Solubility	Soluble in water	Complies
3.	Taste	Bitter	Complies
4.	Odor	Odorless	Complies
5.	Melting point	Range: 216-220°C	215 °C

F1-F9 were carried out with HPMC E15, Methyl Cellulose, Citric acid, Sucrose, Glycerin, SLS and flavor. The films were slightly opaque clear and transparent. The thickness also uniforms. The flexibility also good. The films shown good mechanical properties. According to the assay result the drug was properly loaded in the film. F1-F9 having High-low concentration of polymers. Hence the flexibility of each formulation varies with concentration of polymers.

Table no. 3: Evaluation Parameters.

Formulations	Thickness (mm)	Folding endurance	Tensile strength (g/cm^2)	% Elongation	*In-vitro* disintegration time(sec)
F1	0.58	9	48.41	8	25
F2	0.55	10	51.18	9	28
F3	0.59	13	62.04	11	20
F4	0.51	9	54.25	9	31
F5	0.53	11	53.68	10	35
F6	0.52	11	52.33	8	27
F7	0.55	12	56.45	7	36
F8	0.57	1	57.62	9	32
F9	0.53	9	48.63	10	35

F2 and F7 was formulated with high concentration of HPMC E15 and Methyl cellulose. The appearance of the film was also good but the thickness and disintegration time was more.

F1 and F4 was formulated with HPMC E15 and Methyl Cellulose with low concentration. Both formulation having good flexibility but the thickness was very less.

F5 and F9 was formulated with high concentration of HPMC E15 and low concentration of Methyl Cellulose. The formulated films were more brittleness.

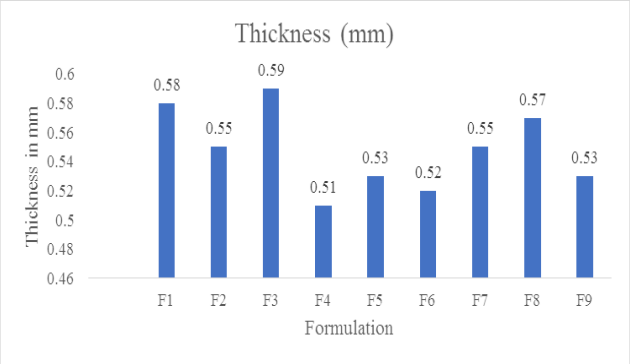

Fig no. 2: Bar chart of Thickness of formulation F1 to F9.

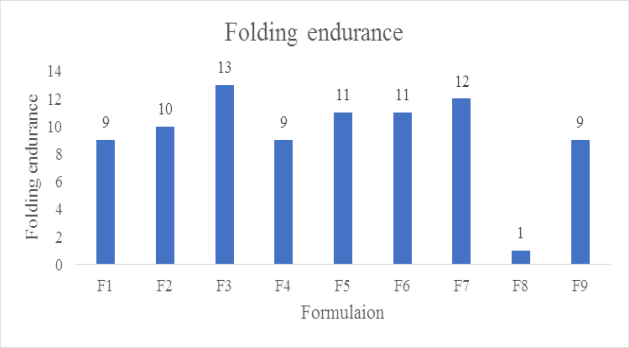

Fig. no. 3: Bar chart of Folding endurance of formulation F1 to F9.

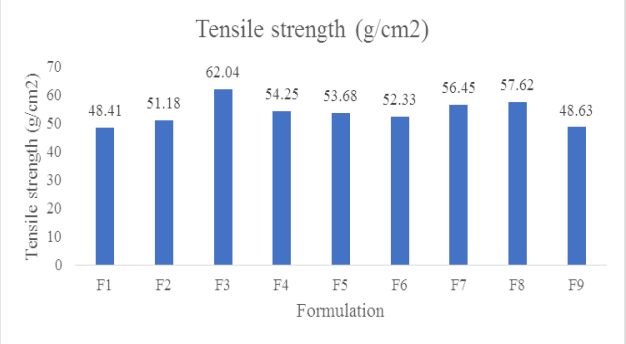

Fig. no. 4: Bar chart of Tensile strength of formulation F1 to F9.

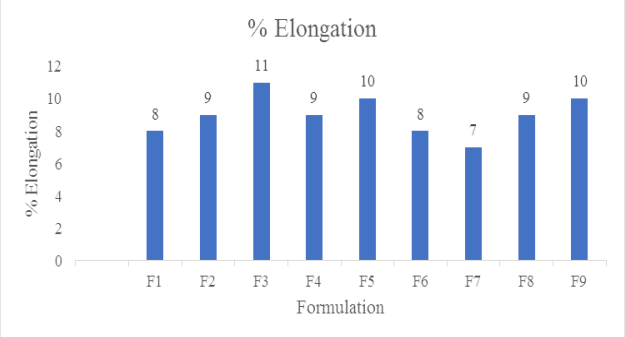

Fig. no. 5: Bar chart of % Elongation of formulation F1 to F9.

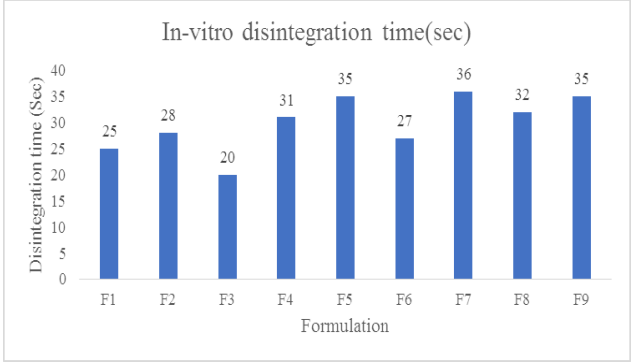

Fig. no. 6: Bar chart of In-vitro disintegration time of formulation F1 to F9.

Table no. 4: Weight variation.

Formulations	Weight variation (mg)
F1	69
F2	68
F3	68.2
F4	69.4
F5	70.2
F6	69.4
F7	68.3
F8	70.6
F9	69.2

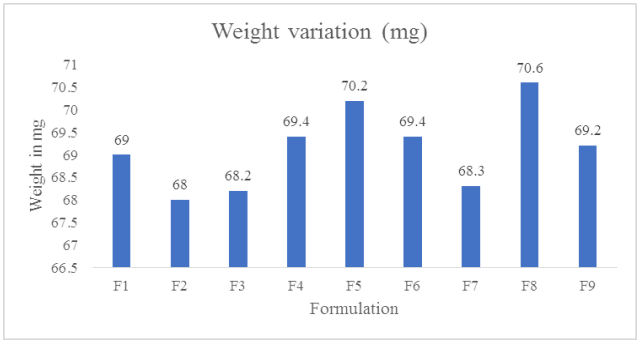

Fig. no. 7: Bar chart of Weight variation of formulation F1 to F9.

Table no. 5: Drug content and Assay.

Formulations	Drug content (mg)	Assay (%)
F1	24.86	97.25
F2	23.25	98.14
F3	25.01	99.87
F4	22.91	98.34
F5	24.55	98.45
F6	23.88	97.22
F7	24.78	98.33
F8	24.63	97.87
F9	23.52	98.12

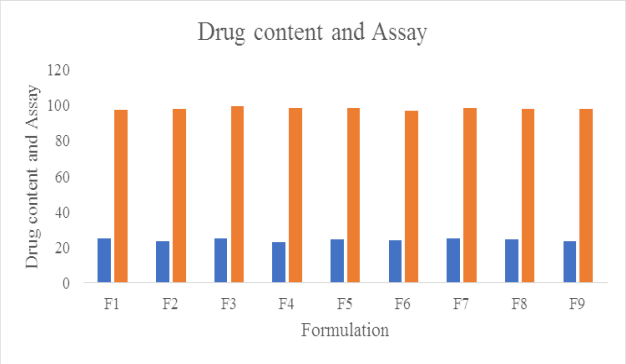

Fig. no. 8: Bar chart of Drug content and Assay of formulation F1 to F9.

Table no. 6: In-Vitro Dissolution of formulation F1 to F9.

Percentage drug released									
Time (Sec)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
60	19	21	17	23	23	21	21	17	20
120	32	36	37	42	41	38	38	34	36
180	52	58	43	58	54	57	55	58	61
240	71	68	78	73	72	69	69	71	70
300	84	86	82	81	79	84	82	82	81
360	93	97	99	95	94	92	97	97	96

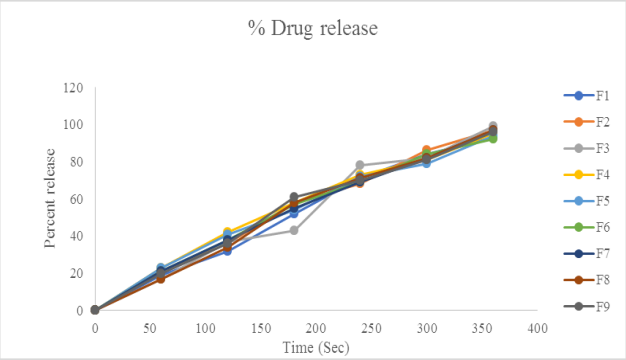

Fig. no. 9: In-Vitro Dissolution (Percent release) of F1 to F9.

Among all the formulations F3 and F6 shown good mechanical properties and less disintegration time of 20 seconds. All the parameters of films were found to be satisfactory. And the dissolution profiles were found to be desirable and reproducible.

The stability studies were performed for about 1 month. No significant changes were observed in the thickness, tensile strength, in-vitro disintegration and in-vitro drug release.

The film (F3) samples evaluated gave maximum release within 6 minutes indicating the rapid drug release profile which entails in faster onset of action for the medicament. Therefore, the oral films have considerable advantage over the conventional dosage forms.

CONCLUSION

The primary objective of this work was to develop a mouth dissolving film with Metformin, along with basic ingredients like polymers, plasticizers, sweetener, saliva stimulating agent and flavor. The films were prepared by solvent casting method. HPMC E15 and Methyl cellulose combination used in film shown good flexibility. Glycerin as plasticizer produced good folding endurance, tensile strength and percent elongation. The optimized formulation (F3) was shown good mouth feel, folding endurance, instant drug release as well as good mechanical properties. The F3, shown less disintegration time of 20 seconds and 99% drug released within 6 minutes. Therefore, rapid drug release was achieved for immediate onset of action which is beneficial when compared to conventional tablet dosage form.

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