

## Formulation, Optimization and In-vitro Evaluation of Fast Dissolving Oral films of Metoclopramide Hydrochloride by Solvent Casting method

Chandrajeet Kumar Yadav<sup>1\*</sup>, Manish Karn<sup>2</sup>,  
Pinki Yadav<sup>3</sup>, Roshan Mehta<sup>4</sup>

Department of Pharmacology<sup>1,2,4</sup>, Universal College of Medical Sciences,  
Bhairahawa, Nepal

**Abstract :** The Present study aimed to prepare fast dissolving oral films (FDFs) of metoclopramide hydrochloride, because of its application in emesis condition where fast onset of action and avoidance of water is highly desirable. Moreover, this dosage form is highly useful in pediatrics, geriatrics and unconscious patients. FDFs were prepared by solvent casting technique with film forming polymers HPMC, PVA & Sodium alginate in varying concentrations with excipients like SLS as surfactant, Glycerol as plasticizer, citric acid as saliva stimulating agent, Sodium Saccharin as sweetening agent. The film of 2×3 cm was prepared by casting into a petridish of calculated size and dried in dryer at temperature 40°C. The In-Vitro evaluation of characteristics like Film Thickness, Weight Variation, disintegration time, dissolution study, surface pH, content uniformity was studied. The best formulation was found to be F5 containing polymer PVA and Sodium alginate in the ratio 2:1, with disintegration time 24 seconds, and dissolution profile of 75% in 60 seconds and 90% in 90 seconds. The content uniformity of all the formulations was found to be within the limit (98-101%). The disintegration time of all the formulations was found to be below 30 seconds except F4 (26 sec.). Thus, fast dissolving Films of Metoclopramide hydrochloride can be successfully formulated and will be used as a novel drug dosage form for paediatric and geriatric with improved patient compliance and enhanced bioavailability.

**Keywords :** FDFs, Metoclopramide, HPMC, PVA, Sodium Alginate, Solvent Casting.

### Introduction

Metoclopramide HCl, chemically known as 4-amino-5-chloro-2-methoxy-N-[(2-diethyl-amino) ethyl] benzamide is a dopamine receptor(D2) antagonist with primary function to stimulate gastric contractions<sup>1</sup>. It increase the tone of lower esophageal sphincter<sup>2</sup>. It is commonly used to treat nausea and vomiting associated with conditions such as uremia, radiation sickness, cancer and the effects of chemotherapy, labor, infection and emetogenic drugs<sup>3,4</sup>.

Metoclopramide is used as a short-term treatment (4 to 12 weeks) for persistent heartburn. It is used mostly for heartburn that occurs after a meal or during the daytime. It is also used in diabetic patients who have poor emptying of their stomach (gastroparesis). Treating gastroparesis can decrease symptoms of nausea, vomiting and stomach/abdominal fullness<sup>5</sup>. It is also used to treat migraine headaches<sup>6</sup> for this it may be used in combination with paracetamol (acetaminophen) or aspirin<sup>7</sup>.

In general, emesis is preceded with nausea and in such condition, it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as fast dissolving films (FDFs). Metoclopramide HCl is an intensely bitter drug<sup>8</sup>; hence, it should be incorporated in the FDFs necessarily with the taste masking agents.

Oral films, a promising novel drug delivery system, are a strip of single or multilayered, mucoadhesive or non-mucoadhesive, thin polymeric films that are intended to deliver active therapeutic moieties either locally or systemically in oral cavity through sublingual, buccal, palatal, or gastrointestinal absorption<sup>9</sup>.

Oral route being one of the most preferred route of drug administration in terms of convenience, cost effectiveness, ease of administration and high patient compliance still it is problematic because of the swallowing difficulty associated with geriatric and pediatric patients who have fear of choking<sup>10</sup>. So, to overcome this disadvantage, bio adhesive mucosal dosage forms have been introduced which includes adhesive tablets, gels, ointments, patches and then in 1925s polymeric films were introduced also known as oral thin films or fast dissolving films or mouth dissolving films or oro-dispersible films or quick disintegrating films and melt in mouth dosage form which was based on the technology of transdermal patches<sup>11</sup>. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oro-mucosal absorption<sup>12</sup>. When put on the tongue, this film disintegrates instantaneously, releasing the drug which dissolves in the saliva. Some drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is significantly greater than that observed for conventional tablets<sup>13</sup>. Since the drug is directly absorbed into the systemic circulation, degradation in the gastrointestinal (GI) tract and first pass effect can be avoided<sup>14</sup>. Today, these are proven to be acceptable for OTC (Over the Counter) medications and are in the early to mid- development stages for prescription drug<sup>15</sup>.

Metoclopramide HCl is highly soluble in water and can be categorized in BCS (Biopharmaceutical Classification System) class III<sup>16</sup>. It is rapidly and well absorbed, oral bioavailability being  $80 \pm 15.5\%$ .<sup>17</sup> since the usual adult dose is 5-10mg this forms an excellent candidate for oral FDF formulation<sup>24</sup>.

## Materials and Methods

### Material

Metoclopramide hydrochloride (API) was provided as a gift from TIME pharmaceuticals (p.) Ltd. Gairidkot 10 Nawalparasi Nepal. All other excipients like HPMC, PVA, Sodium Alginate, glycerol, SLS, Sodium Saccharin, Citric acid & peppermint oil were available in college laboratory.

### List of chemicals

S.N	Materials	Property	Manufacturer
1.	Metoclopramide HCL	API	Vaikunth Chemicals/STC
2.	HPMC	Film Forming Polymer	Kemphasol.
3.	PVA	Film Forming Polymer	SDFC Fine chem. Limited.
4.	Sodium Alginate	Film Forming Polymer	Kemphasol
5.	Glycerol	Plasticizer	SDFC Fine chem. Limited
6.	SLS	Surfactant	SDFC Fine Chem. Limited
7.	Citric Acid	Saliva Stimulating Agent	Avantor
8.	Sodium Saccharin	Sweetening Agent	SDFC

9.	Xanthan Gum	Stabilizing Agent	Kemphasol
10.	Pippermint oil	Flavouring Agent	SDFC
11.	Potassium Dihydrogen Phosphate	Buffer	Merck

## Methods

### Preparation of fast dissolving films

### 1. Calculation of drug loaded in the film:

The petri dish diameter is 9.8cm.

Total surface area of petri dish was 75.42 cm<sup>2</sup>.

Each film surface area =  $2 \times 3 = 6\text{cm}^2$ .

Number of films in batch =  $75.42/6 = 12.57$  films.

The amount of drug in each patch is  $12.57 \times 5 = 75\text{mg}$ .

## 2. Formulation of fast dissolving oral films

Six formulations with different composition as shown in table 1 were prepared using solvent casting method. All the ingredients were weighed accurately. The solvent used was distilled water. The water-soluble polymers (HPMC, PVA & Sodium Alginate) were first dissolved in little amount of solvent while stirring. The other excipients (glycerol, SLS, Citric Acid, Sodium Saccharin) were mixed in another beaker with little amount of solvent while stirring. Both the solution was mixed and triturated well in a mortar and pestle. The viscous solution was then passed through #60 sieve. Finally, the solution of API was mixed in the resulting solution. The final mixture was then again stirred for 5 minutes and kept aside for removal of air bubbles for 1 hour. The solution was then casted onto a petridish and allowed to dry in the dryer for 24 hours. The dried film was cut in the size of 2\*3 cm<sup>2</sup> and carefully packed in the aluminum foil of required size.

**Table (1): Composition of MCP HCl fast dissolving film in each formula**

S. N.	Materials(mg)	Property	F1	F2	F3	F4	F5	F6
1	Metoclopramide HCl	API	62.8	62.8	62.8	62.8	62.8	62.8
2	HPMC	Polymer	135.85	135.85	-	90.5	-	-
3	PVA	Polymer	135.85	-	135.85	90.5	181.13	90.5
4	Sodium Alginate	Polymer	-	135.85	135.85	90.5	90.5	181.13
5	Glycerol	Plasticizer	82.5	82.5	82.5	82.5	82.5	82.5
6	SLS	Surfactant	40	40	40	40	40	40
7	Citric Acid	Saliva Stimulating agent	33	33	33	33	33	33
8	Sodium Saccharin	sweetener	30	30	30	30	30	30
9	Xanthan Gum	Stabilizer	30	30	30	30	30	30
10	Peppermint oil	Flavoring agent	q.s	q.s.	q.s.	q.s.	q.s.	q.s.
11	TOTAL	550	550	550	550	550	550	550

## Evaluation of Post Formulation Parameters<sup>20,21,22</sup>

### Thickness

The three films of each formulation (F1-F6) were measured for its thickness at 5 different positions with the help of digital Vernier caliper.

### Weight Variation

Six films from each formulation were weighed on a digital balance and mean  $\pm$ SD was calculated.

### Surface pH

For the evaluation of the pH of the surface, a film was dissolved in 10 ml of distilled water in the container and the surface pH was measured by using a pH meter.

### Content Uniformity

One sheet of film from each formulation was dissolved in simulated salivary fluid pH 6.8 in a flask of 25 ml, 0.5 ml of the solution was then diluted with same solution to 10 ml. According to the USP standards, the contents of preparations should lie between the limits 98 to 101%. The results were expressed as mean of six determinations of each formulation and mean $\pm$ S.D calculated. The drug content was determined by using a standard calibration curve of Metoclopramide at wavelength 273 nm<sup>23</sup>.

### Disintegration time

Six Films from each formulation were put in each tube of the basket, then the tool was run by using the medium of pH 6.8 simulated saliva solution at the temperature of  $37 \pm 0.5^\circ\text{C}$ . Disintegration time was observed in each film.

### Dissolution Study

The dissolution test was performed with USP type II dissolution test apparatus with rotational speed 50 rpm, dissolution medium pH 6.8 simulated saliva solution, 500 ml at  $37 \pm 0.5^\circ\text{C}$ . A film was put in dissolution apparatus. 5 ml solution was taken at the 15, 30, 45, 60,75 and 90 seconds. The same medium was replaced with 5 ml so that the volume remained. Absorbance was determined spectrophotometrically at 273 nm. This process was repeated for six films from each formulation.

## Result

### Post Formulation Parameters

#### Thickness

Three films from each batch of the formulation were taken randomly and measured for thickness at four corners and center with the help of digital vernier caliper. the result was expressed in the form of mean $\pm$ S.D. The maximum thickness ( $0.063 \pm 0.005$  mm) was found in F4 and the minimum thickness ( $0.041 \pm 0.003$  mm) was found in F2 formulation.

#### Weight Variation

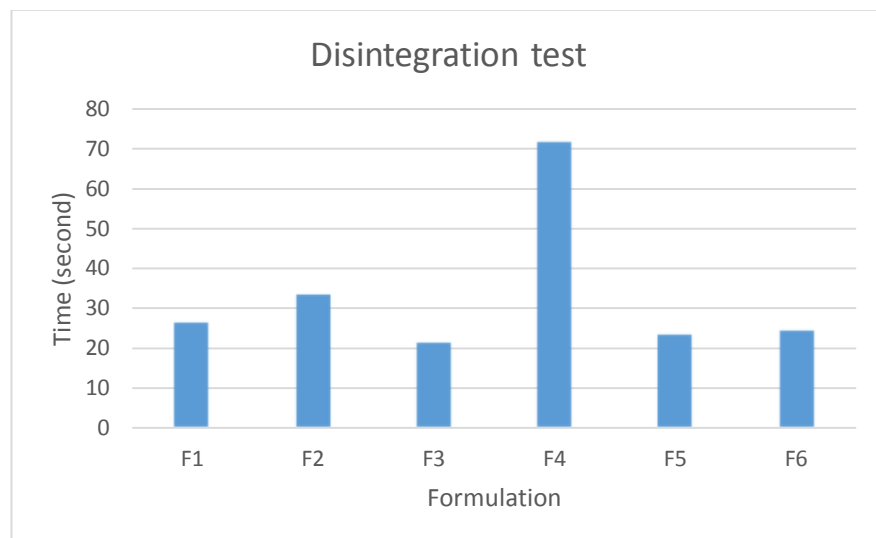
The weight of six films from each formulation was taken and expressed in the form of mean  $\pm$  S.D. The maximum weight ( $4.251 \pm 0.005$  mg) was found to be of F2 and minimum weight ( $3.090 \pm 0.003$  mg) was found to be of F6.

#### Surface pH

One film from each formulation was dissolved in 10 ml of distilled water in a container and pH was measured. It was found in the range of 7.26 in F1 to 7.51 in F4. This indicates that the film wound not irritate buccal mucosa as pH is near to neutral pH.

### Disintegration time

Six films from each batch was taken and put in each tube of the basket. The apparatus was run by using the medium of pH 6.8 simulated saliva solution at the temperature of  $37 \pm 0.5^\circ\text{C}$ . the maximum disintegration time (26 seconds) was found in F4 and minimum disintegration time (22seconds) was found in F3 formulation.

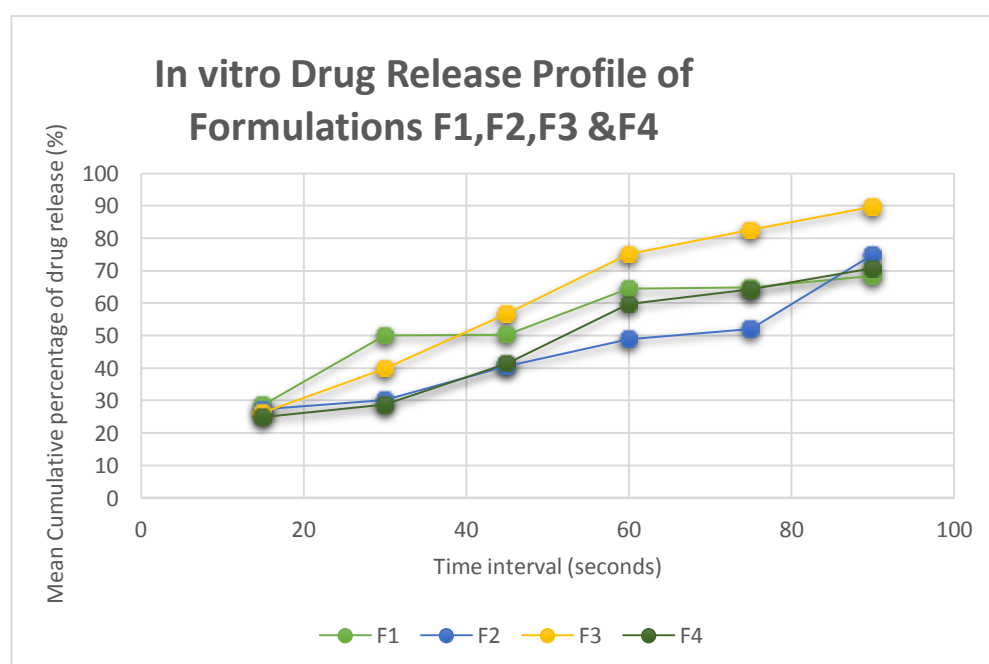


**Fig 1: Disintegration time**

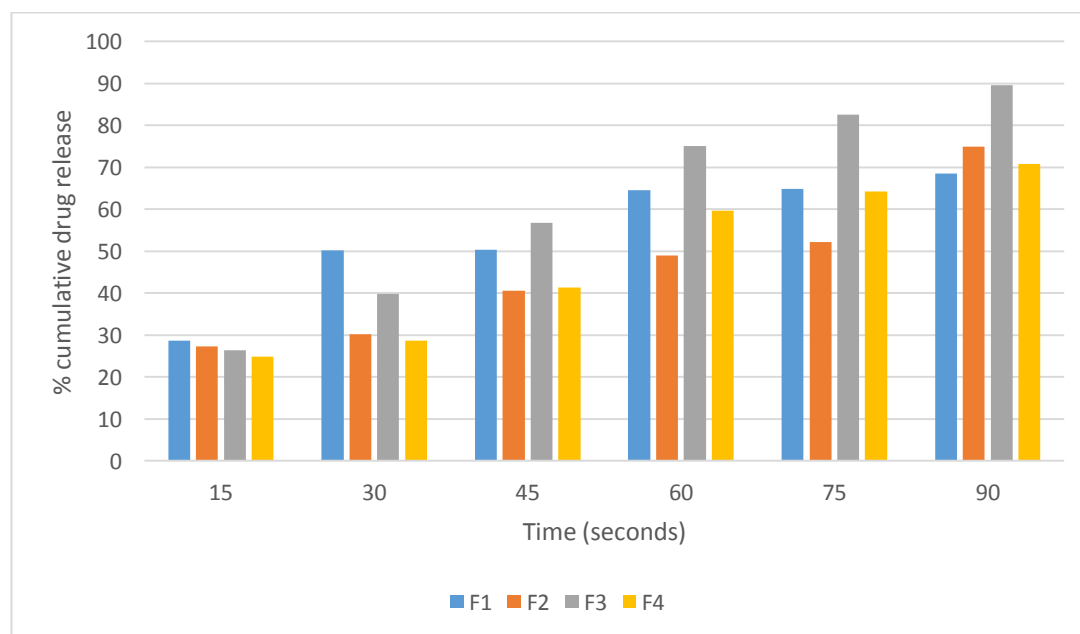
### Dissolution study

The water-soluble hydrophilic polymers like HPMC K4M, PVA and Sodium alginate dissolve rapidly and introduce porosity. The void volume is thus expected to be occupied by the external solvent which diffuses into the film and thereby accelerate the dissolution<sup>18,19</sup>.

Invitro dissolution and release studies of all the formulations was performed using pH 6.8 simulated salivary fluid as dissolution medium and drug concentration was measured spectrophotometrically at 273 nm by using a calibration curve. The result is shown in the graph below.

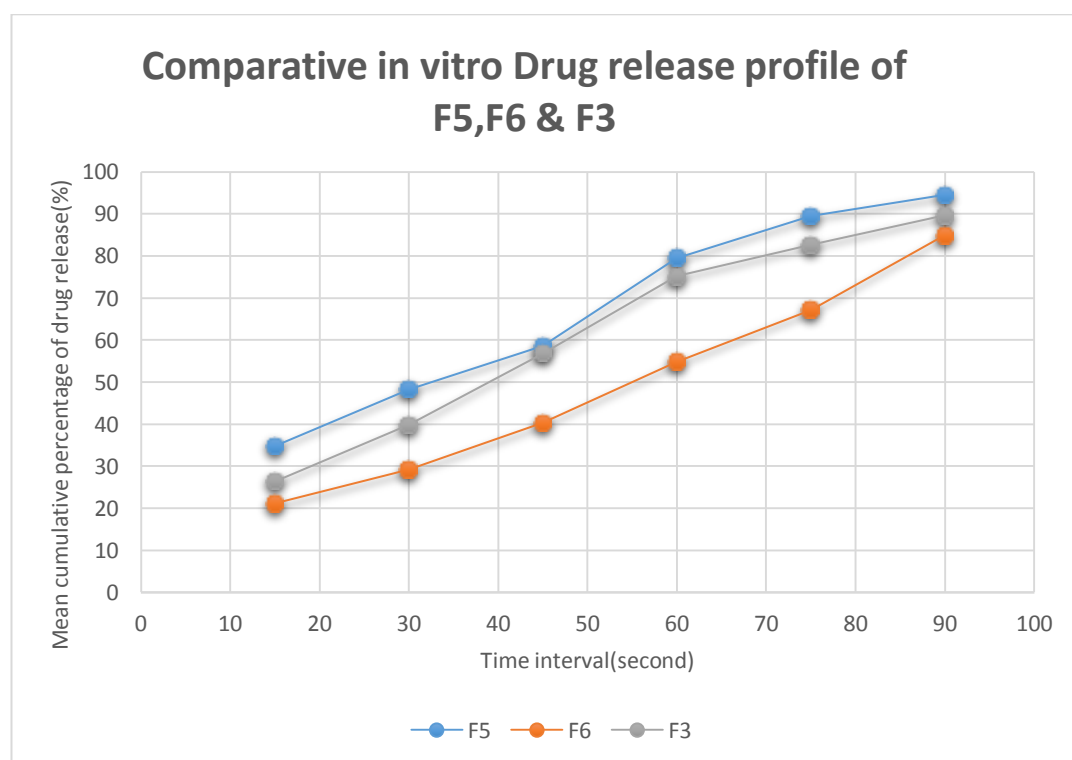


**Figure 2: Comparative line graph of dissolution Profile of F1, F2, F3, F4**

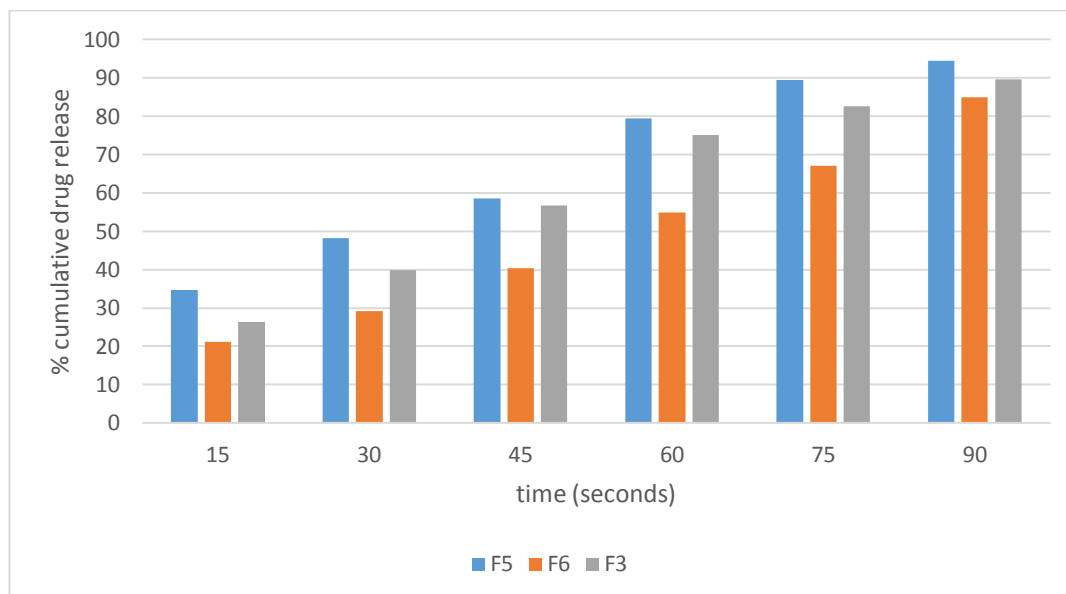


**Figure 3: Comparison of dissolution profile of F1, F2, F3, F4**

The formulation F3 containing PVA and sodium alginate in the ratio 1:1 showed better release profile than others showing more than 75% of drug release in 60 seconds and nearly 90% in 90 seconds. Further two batches of formulation F5 and F6 were prepared to investigate the optimized ratio of the polymer combination and the in-vitro dissolution profile was studied. The result is shown in the following figure.

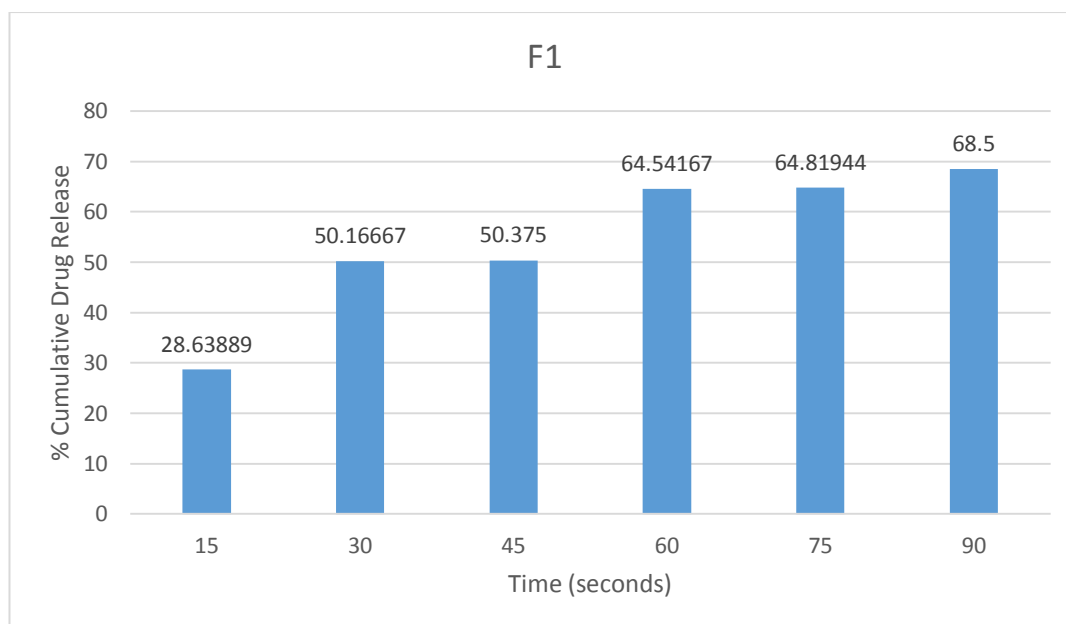


**Figure 4 : Comparative drug release profile of optimized formulation**

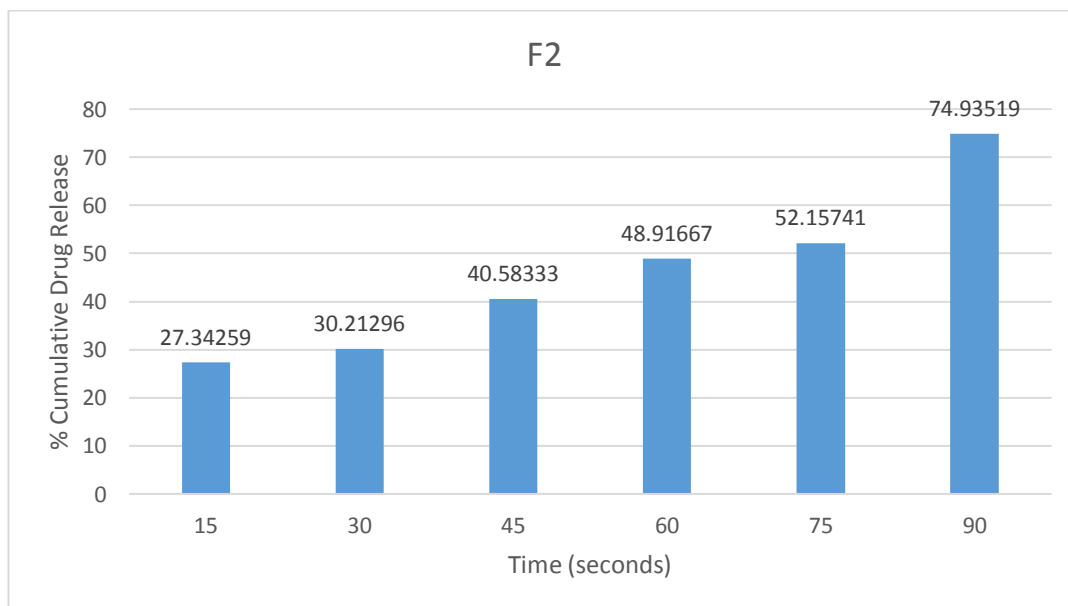


**Figure 5: comparison of drug release profile of F5, F6, F3**

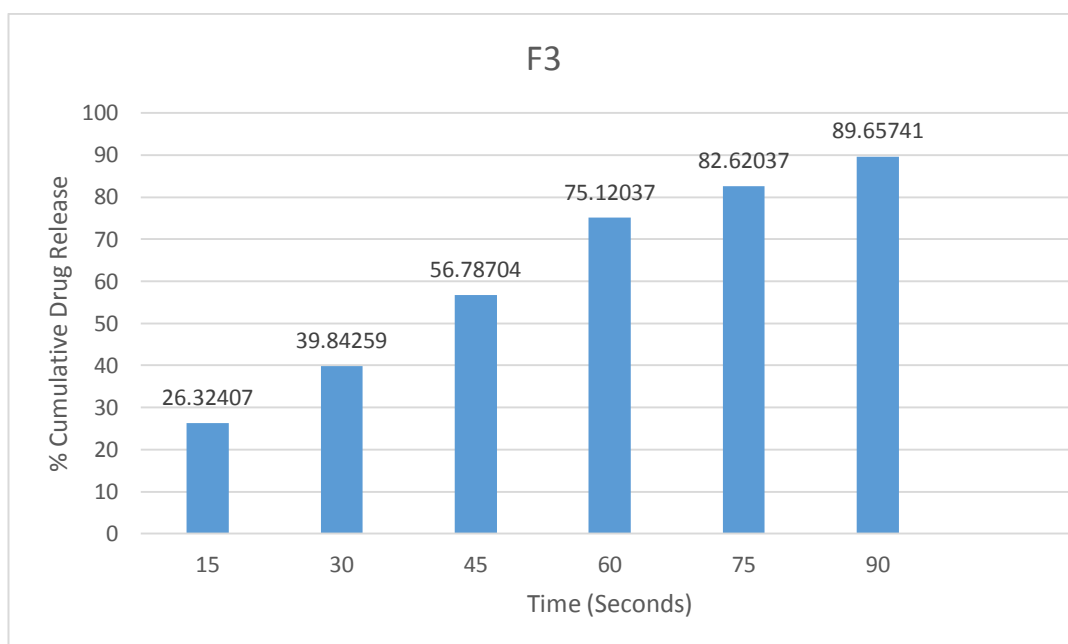
The formulation F5 containing PVA: Sodium alginate in the ratio 2:1 showed even better release profile having more than 79% drug release at 60 seconds and nearly 95% drug release at 90 seconds.



**Figure 6: Drug Release Profile of F1.  $P < 0.05$  (0.008358)**

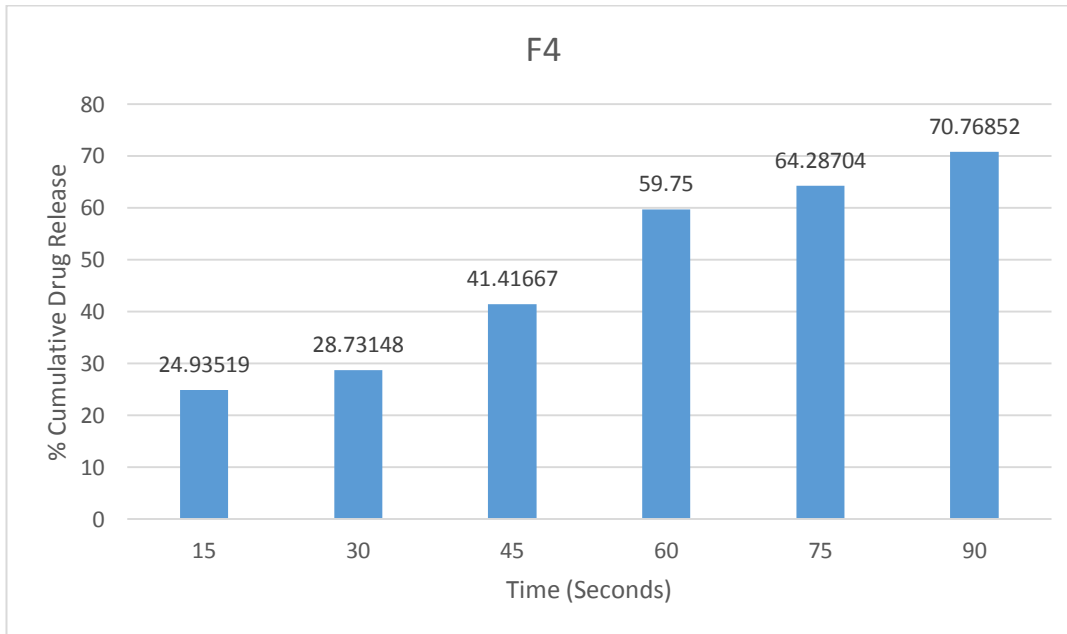


**Figure 7: Drug Release Profile of F2.**  $P < 0.05$  (0.002352)

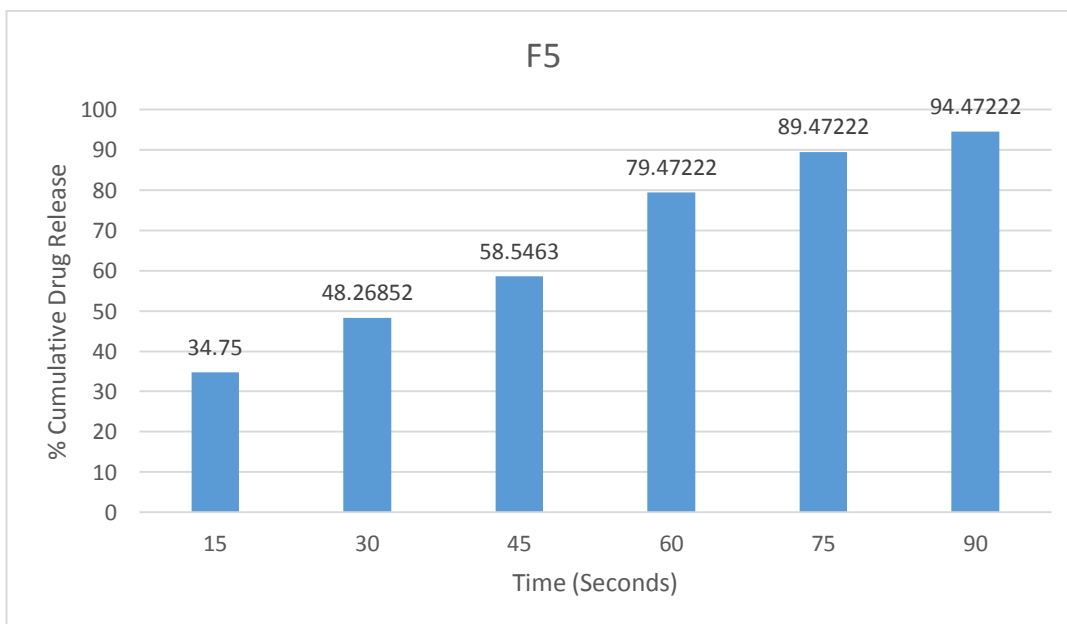


**Figure 8: Drug Release Profile of F3.**  $P < 0.05$  (0.000281)

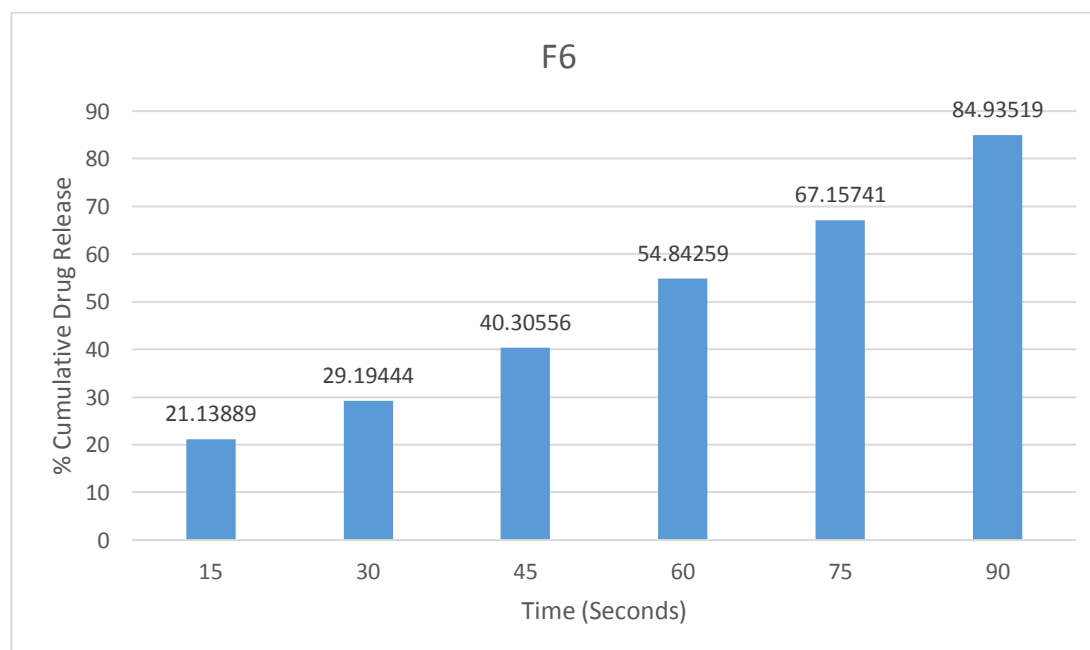




**Figure 9: Drug Release Profile of F4.  $P < 0.05$  (0.000627)**



**Figure 10: Drug Release Profile of F5.  $P < 0.05$  (0.000229)**



**Figure 11: Drug release profile of F6.  $P < 0.05$  (0.000281)**

### Content Uniformity/ Assay

All the films were found to contain an almost uniform quantity of the drug, as per content uniformity studies indicating reproducibility of the technique. The average metoclopramide content in all the film preparations was found to be in the range 98%- 101% except F4 only showed assay of 96.78%. Thus, the preparations met the criteria of USP content uniformity (98.0%-101.0%). On this basis, it was found that the drug was dispersed uniformly throughout the film of 6 cm<sup>2</sup> (3 x 2 cm).

### In vitro test result of other parameters

	Thickness (mm)	Weight (mg)	Surface pH	Content Uniformity (%)
<b>F1</b>	0.053±0.004	3.525±0.003	7.26	98.7314 %
<b>F2</b>	0.041±0.003	4.251±0.005	7.41	98.638%
<b>F3</b>	0.055±0.004	3.258±0.004	7.28	99.1944 %
<b>F4</b>	0.063±0.005	3.50±0.002	7.51	96.7825 %
<b>F5</b>	0.054±0.004	3.390±0.002	7.34	98.1759 %
<b>F6</b>	0.053±0.006	3.090±0.003	7.36	100.4907 %

### Discussion

Distilled water was selected as solvent as all the selected excipients and API was soluble in water in contrast to alcoholic or hydro-alcoholic solvent which posed the solubility problem. Coloring agent titanium dioxide was not used in the formulation as it is insoluble in water and showed incompatibility. The dissolution profile of F3 formulation was found to be better than formulations F1, F2 and F4 and hence the polymer combination PVA and Sodium alginate in the ratio 1:1 was found to be best formulation. On this basis formulation F5 and F6 were formulated with same polymer differing the combination ratio. Formulation F5 containing PVA: Sodium alginate (2:1) showed the better drug release profile than all other formulations and was concluded as optimized formulation.

Little modification in the formulation process was done than the usual process. The excipients solution was

trituated in mortar and pestle and passed through #60 sieve to remove the grittiness and to form well mixed viscous solution which resulted in the smooth texture of all the batches of film otherwise the films containing sodium alginate showed grittiness and the appearance was not smooth. All the formulation Batches after this modification showed more pleasant and viscous solution at the time of pouring into mould and the resulting film after drying was smooth and uniform.

Simulated salivary fluid of pH 6.8 was selected as the dissolution medium to mimic the oral environment to some extent and since the average oral pH of a healthy individual is nearly 6.8.

The main aim of this study was to find the optimized combination ratio of the polymers used, to determine the formulation having best in vitro disintegration and dissolution profile. Polymers were used in combination (not alone) to improve the organoleptic characteristics. PVA and sodium alginate in the ratio 2:1 gave the best results.

Films containing HPMC did not show good drug release profile as the HPMC used was of medium viscosity grade (K4M), glass transition temperature  $T_g = 191^\circ\text{C}$ <sup>25</sup> which formed tough film delaying the solubility and hence decreasing the drug release rate. Thus, it can be concluded that despite the good film forming property of HPMC the grades of lower viscosity is particularly useful for flash release films as it has lower glass transition temperature ( $T_g$ ).

PVA is a synthetic polymer with good film forming property ( $T_g = 85^\circ\text{C}$ )<sup>26</sup> and Sodium alginate is a biomaterial which possess moderate film forming characteristics ( $T_g = 115.5^\circ\text{C}$ )<sup>26</sup>. Both these polymers are biodegradable and are non-toxic and non-irritant to oral mucosa hence this combination forms an excellent choice of polymers for fast dissolving oral films.

Glycerol was used as plasticizer to decrease the glass transition temperature ( $T_g$ ) of the polymer matrix by incorporating its small molecules in the polymer matrix which improves flexibility and reduce brittleness of the film and helps in rapid disintegration of the film when kept in oral cavity and imparts good mouth feel.

Citric acid was used as saliva stimulating agent which increase the rate of saliva secretion and helps in rapid dissolution of the film.

Sodium saccharin was used as sweetening agent and peppermint oil was used as flavouring agent to mast the bitter taste of the drug and increase patient compliance.

Since, Metoclopramide undergoes enzymatic metabolism via oxidation as well as glucuronide and sulfate conjugation reactions in the liver, the oral absorption will avoid first pass metabolism and bioavailability will be increased.

Special consideration should be laid on packaging of FDFs since it is highly hydrophilic and subjected to degradation in environmental condition.

FDFs are novel drug delivery system and have recently became the part of European Pharmacopoeia monograph under the heading "Oromucosal Preparations". USFDA has approved some FDFs on the basis of bioequivalence with fast dissolving tablets. Hence this is the need of time for further research and documentation in this sector as this has the potentiality to serve as excellent drug delivery system for pediatric and geriatric use and would improve patient compliance as well. Necessary Research and documentation is required to incorporate this dosage form into Nepalese national Formulary and the increase in industrialization in pharmaceutical sector in the country would serve as the platform to develop and market such products leading towards the goal of self-reliant in medicine production to fulfill the health care needs of the population.

## Conclusion

According to the result obtained from the research work, the formulation prepared from the polymers PVA and Sodium alginate showed better dissolution rate and disintegration time when compared with HPMC containing formulations of the prepared Fast Dissolving Oral Films (FDFs).

The fast dissolving films with the use of different Film forming polymers had been shown as a successful approach to improve the disintegration time and dissolution rate of Metoclopramide hydrochloride. Selection and combination of film forming polymers and pharmaceutical excipients play an important role in enhancement of dissolution rate, buccal absorption, improved bioavailability and patient's compliance.

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