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Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2011, 3(4):636-646

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Flash release oral films of metoclopramide hydrochloride for pediatric use: Formulation and *in-vitro* evaluation

S. Raju [*1], P. Sandeep Reddy [1], V. Anirudh Kumar [1], A. Deepthi [1], K. Sreeramulu Reddy [2] and P.V. Madhava Reddy [3]

[1]*Vijaya College of Pharmacy, Munaganoor, Hayath Nagar, Hyderabad, Andra Pradesh, India*
[2]*Shantha Biotechnics Limited, Basheer Bagh, Hyderabad, Andhra Pradesh, India*
[3]*Sarada College of Pharmaceutical Sciences, Kondakavuru, Narasaraopet, Andhra Pradesh, India*

ABSTRACT

The ultimate goal of any drug delivery system is the successful delivery of the drug to the body; however, patient compliance must not be overlooked. Fast dissolving drug delivery systems, such as, mouth dissolving films, offer a convenient way of dosing medications, not only to special population groups with swallowing difficulties such as children and the elderly, but also to the general population. Mouth dissolving Films are the novel dosage forms that disintegrate and dissolve within the oral cavity within a minute, without needing water or chewing. A novel flash release oral film drug delivery system for the treatment of emesis in paediatrics *was developed for immediate oral delivery of metoclopramide which is an excellent antiemetic drug. Two metoclopramide film formulations naming F-1 and F-2 were prepared by solvent casting technique using two water soluble polymers, hydroxypropyl methyl cellulose, and carboxy methyl cellulose. Infrared analysis revealed no interaction between Metoclopramide and polymers. The prepared films were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, surface pH and In-vitro release. Formulation F1 released 99.40% of drug within 30 sec and was considered as best formulation. This case study showed that hydroxypropyl methyl cellulose was the most suitable film-forming material for metoclopramide -loaded films, providing fast dissolution films that were not sticky and were easy to handle.*

Key words: Metachlopramide; Oral delivery; Mouth Dissolving Films; flash release; I*n-vitro*.

INTRODUCTION

Despite of tremendous advancements in drug delivery, Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms[1] due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and, most importantly, patient

compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture [2].The aforementioned advantages of drug administration via the oral cavity offer new possibilities in the administration of drugs to "problematical" subpopulations like children and the elderly. These patients have special drug administration requirements as they are often unable to swallow solid dosage forms (e.g. tablets, capsules). Poor taste can also lead to medication being refused or spat out. Furthermore, the pediatric subpopulation is a very heterogeneous group. Fast-dissolving solid drug dosage forms for application onto the oral cavity for the Pediatric population seem to be very appropriate, especially in preterm and term newborn infants [3]. Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water or chewing. More recently, fast-dissolving films which dissolve/disintegrate in the mouth within a few seconds without additional water and the need to swallow are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients' fear of chocking and overcome patent impediments [4].Therefore, they are very suitable for pediatric and geriatric patients, bedridden patients or patients suffering from dysphagia, Parkinson's disease, mucositis or vomiting [5]. This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half life and bioavailability enhancement of drugs [6]. Metoclopramide was chosen as model drug for which a need for child-appropriate (5mg) drug formulations exists. The drug was selected based on a high frequency of prescribing, an appropriate indication and age for this new dosage form, an adequate dosage on the basis of the limited drug-loading capacity of the films and adequate bioavailability of the drug after application. Metoclopramide Hcl as acid salt seemed to be appropriate.

Metoclopramide hydrochloride is a white crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5- chloro-N-[2-(diethylamino) ethyl]-2-methoxy benzamide monohydrochloride monohydrate, and is used as an anti-emetic in the treatment of some forms of nausea and vomiting and to increase gastrointestinal motility. Metoclopramide Hydrochloride blocks dopamine receptors and (when given in higher doses) also blocks serotonin receptors in chemoreceptor trigger zone of the CNS; enhances the response to acetylcholine of tissue in upper GI tract causing enhanced motility and accelerated gastric emptying without stimulating gastric, biliary, or pancreatic secretions; increases lower esophageal sphincter tone[7].

EXPERIMENTAL SECTION

Instruments

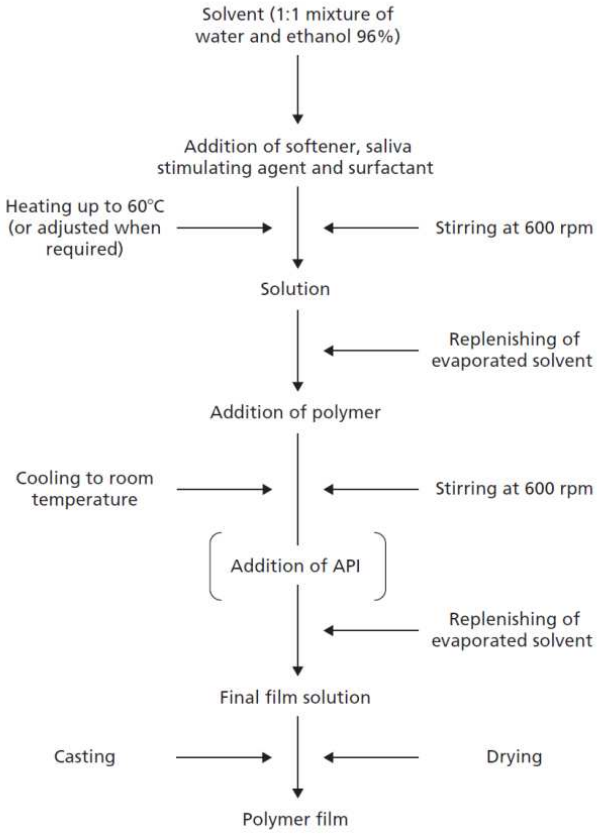
Shimadzu double beam UV-visible spectrophotometer (model 1700) with 1 cm matched quartz cuvettes were used for all absorbance measurements. IR 8400S, Shimadzu, Japan was used for Drug polymer compatibility study. Digimatic & Vernier Caliper *(*Mitutoyo 550-203-10, Mitutoyo, Japan*)* was used to measure thickness; analytical balance (Shimazdu AX200, Japan**)** was used for weighing the samples and films.

Materials

Metoclopramide Hcl was obtained as a gift sample from Ipca Laboratory (Mumbai, India). HPMC E6 was obtained from Colorcon Asia Ltd, India; Sodium Carboxy Methylcellulose (SCMC) was obtained from Cellulose Pharma Chem., Jalgaon, India. Citric acid, Glycerol, Tween-80, and Mannitol, were obtained from S.D fine chemicals Ltd., Mumbai, India; and

Saccharin sodium was obtained from Zhengzhou Natural Chemical Co., Ltd. China. And all other materials used in the study were of analytical grade.

Figure 1 Method for preparation of oral films.



Drug polymer compatibility [8]

Pure drug (Metoclopramide) and polymers were subjected to FTIR studies alone and in combinations. 3 mg of pure drug / combination of drug - polymer were triturated with 97 mg of potassium bromide in a smooth mortar. The mixtures were placed in the sample holder and were analyzed by FTIR to study the interference of polymers with the drug.

Preparation of cast film containing Metoclopramide

Hydroxypropyl methyl cellulose and Carboxy methyl cellulose are known for their good strip-forming properties and has excellent acceptability [9, 10]. For the fabrication of films, glycerol was used as plasticizer, Sodium bicarbonate as Disintegrating agent, Citric acid as an anti oxidant and saliva stimulating agent, Tween-80 as surfactant and Saccharin sodium was as a sweetener. Metoclopramide films were prepared by solvent casting technique according to a standard scheme. **FIG-1**. First the water soluble polymers are dissolved in water and the drug along with other recipients is dissolved in suitable solvent (water & 96% alcohol at 1:1 ratio) then both the solutions are mixed and stirred and finally casted in to Glass moulds and dried.

Formulations were designed as shown in the **Table-I**. The table shows the detailed compositions of film formulations which are used in the present study. The loading of the oral wafers with API

requires the calculation of mass per film strip to achieve the desired drug-load of 5 mg Metoclopramide Hcl. Initially the mass of API per batch was calculated by using the formula. **(Equ.1)**

$$\text{Equ.1} \qquad m_{\text{API in } b} = \left(\left(\frac{m_{\text{API in } f}}{con} \right) . \left(\frac{A_b}{1000 . A_f} \right) \right)$$

A_b = *batch size [cm²]*
A_f = *size of one film [cm²]*
Con = *content of API [% / 100]*
$m_{ing\ in\ b}$ = *mass of ingredient in batch [g]*
$m_{ing\ in\ f}$ = *mass of ingredient in one film [mg]*

Table-I: Composition of the formulations

Formulation code	F1	F2
Drug	1.26	1.26
HPMC E6	10.33	-
SCMC	-	4.57
Sodium Bicarbonate	1.30	1.30
Mannitol	2.14	2.28
Glycerol 85%	0.86	0.91
Citric acid	0.43	0.46
Tween 80	0.07	0.08
Saccharin sodium	0.29	0.30
Alcohol 96%	42.16	44.42
Water	42.16	44.42
Values are in percentage %		

A drug-load of 5mg Metoclopramide Hcl per oral wafer has been achieved. The content of the Metoclopramide Hcl base was determined by IR & UV analysis and amounted 99.85 % related to the reference, Metoclopramide Hcl. The batch size was 1500 cm² and each film strip had an area of 6 cm², with a rectangle shape measuring 2 x 3 cm. The factor 1000 is the conversion factor from [g] into [mg].

In a next step the amount of each ingredient that should be contained in a single film strip was calculated by using the formula **(Equ.2)**

$$\text{Equ.2} \qquad m_{\text{ing in } f} = \left(\frac{m_{\text{ing in b}}}{\left(\frac{A_b}{A_f} \right)} \right) . 1000$$

A_b = *batch size [cm²]*
A_f = *size of one film [cm²]*
$m_{ing\ in\ b}$ = *mass of ingredient in batch [g]*
$m_{ing\ in\ f}$ = *mass of ingredient in one film [mg]*

Finally, the mass of one film strip can be calculated from the amount of each ingredient per film strip excluding the solvent, given that the solvent is completely evaporated.

$$\text{Equ.3} \qquad m_f = \sum_{1}^{n} m_{\text{ing in f}} - m_{sol\ \text{inf}}$$

m_f = *mass of one of film [mg]*
$m_{\text{ing in f}}$ = *mass of ingredient in one film [mg]*
$m_{\text{sol in f}}$ = *mass of solvent in one film [mg].*

Evaluation of films

Identification

The films containing Metoclopramide were subjected to Infra Red studies for identification and to study drug polymer compatibility. (IR 8400S, Shimadzu, Japan).The KBr disk method was used for preparation of samples and the spectra were recorded over the wave number 4000 to 400 cm^{-1}. [11]

Morphological properties

Properties such as homogeneity, color, transparency and surface of the oral films were evaluated by visually inspection. [12]

Uniformity of dosage units of the oral strips

The content uniformity of dosage units of the oral film preparation was tested for Metoclopramide Hcl using UV spectroscopy. 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±S.D calculated. The drug content was determined by using a standard calibration curve of Metoclopramide [13]. **[Figure-5]**.

Preparation of standard calibration curve of Metoclopramide in phosphate buffer solution (6.8pH)

100mg of Metoclopramide was accurately weighed and dissolved in phosphate buffer 6.8 pH into a volumetric flask and the volume made upto 100ml with the same. 10 ml of this stock solution was taken and made up to 100 ml with phosphate buffer solution, which gives 100 mcg/ml concentrations (working standard). From this working standard, aliquots of 1.0, 3.0, 5.0, 7.0, 9.0 and 11.0 ml was pippeted into 50ml volumetric flask and the volume was made upto 50 ml with phosphate buffer 6.8 pH. The absorbance of the diluted solution was measured at 273 nm against reagent blank (phosphate buffer 6.8 pH) in triplicate and a standard plot was drawn using the mean data obtained. The correlation coefficient was calculated by linear regression analysis. The absorbances of the above concentration are shown in **Table-III.**

Film mass

The mass of films was determined by an analytical balance (Shimazdu AX200, Japan**).** This test was performed on six films of each formulation and mean±S.D calculated.

Film thickness

Film thicknesses were determined using the Digimatic & Vernier Caliper *(*Mitutoyo 550-203-10, Mitutoyo, Japan*).* Each wafer was measured at five positions (central and the four corners) and

the mean thickness was calculated. This test was performed on six films of each formulation and mean±S.D calculated.

Folding endurance study

It was measured manually for the prepared fast dissolving film (3 X 2 cm). A strip was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. This test was performed on six films of each formulation and mean±S.D calculated [14].

Surface pH study

The surface pH of fast dissolving strip was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral strip was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. This study was performed on six films of each formulation and mean±S.D calculated [15].

In vitro disintegration studies:

Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film. The film as per the dimensions (3x 2 cm) required for dose delivery was placed on a stainless steel wire mesh placed in a petridish containing 10 ml phosphate buffer pH 6.8. Time required for the film to break was noted as *in vitro* disintegration time. This test was performed on six films of each formulation and mean±S.D calculated [16].

Dissolution and Drug release

Dissolution test of Metoclopramide Hcl films was performed using (900 ml; phosphate buffer pH 6.8 with USP dissolution apparatus II (Labindia, Mumbai, India) at 50 rpm and 37±0.5 °C temperature. The drug release was analyzed spectrophotometrically at λ max 273 nm using ultraviolet (UV) spectrophotometer (Shimadzu model no: 1700) by using a calibration. One film was placed into each vessel and Test sample (5 mL) was withdrawn at particular time interval (10, 20, 30 and 40 Sec) and replaced with fresh dissolution media maintained at 37±0.5 °C). This test was performed on six films of each formulation and mean±S.D calculated [17, 18, 19, 20, 21].

RESULTS AND DISCUSSION

Oral films of metoclopramide were prepared using water soluble polymers HPMC-E6, and sodium CMC. Glycerol was used as plasticizer. Sodium bicarbonate as Disintegrating agent, Citric acid as an anti oxidant and saliva stimulating agent, Tween-80 as surfactant and Saccharin sodium was as a sweetener. The drug in the films was identified and were characterized for their physical characteristics, thickness, folding endurance, surface pH, drug content uniformity and release characteristics. **[Table -II].**

Identification and purity

The IR spectra of pure drug **(Figure-2)** shows prominent peaks at 3305.76 cm $^{-1}$, 3396.41 cm-^{1}, 1596.95 cm^{-1}, 693 cm^{-1} corresponding to the -NH stretching, -OH stretching, C=O and C-Cl stretching respectively. The spectrum of the drug was compared with spectra provided for the reference drug in USP.The characteristic peaks of drug matched with the reference which confirms the purity of the drug.

Table -II: Evaluation of fast dissolving films of Metoclopramide hydrochloride

Formulation code	F1	F2
Drug content (%)	99.40 ± 0.24	98.71±1.22
Film mass (mg)	57.29±0.29	57.03±0.38
Film thickness (mm)	0.208±0.001	0.209±0.001
Folding endurance	199.33±2.16	191.16±3.06
Disintegration time(Seconds)	20.23±0.75	22.41±0.57
Surface $_{p}$H	6.89±0.10	6.83±0.09

Figure 2: IR spectrum of pure drug showing prominent peaks

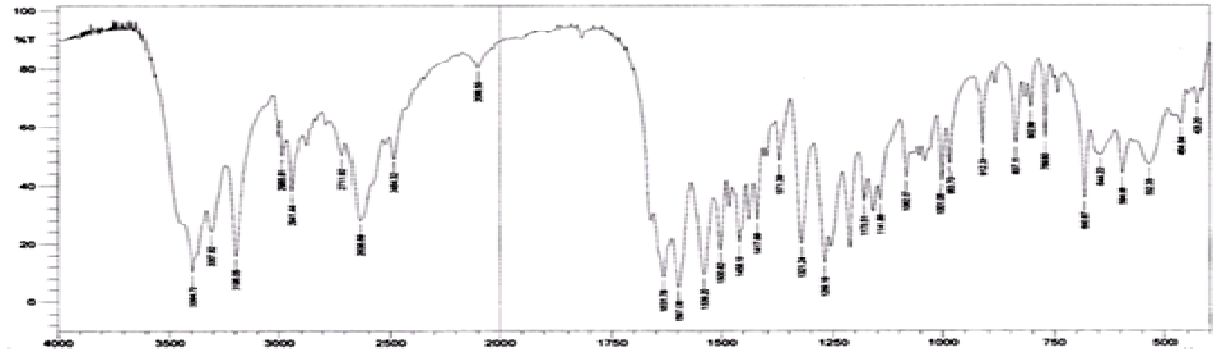


Figure 3: IR spectrum of drug along with SCMC showing prominent pea

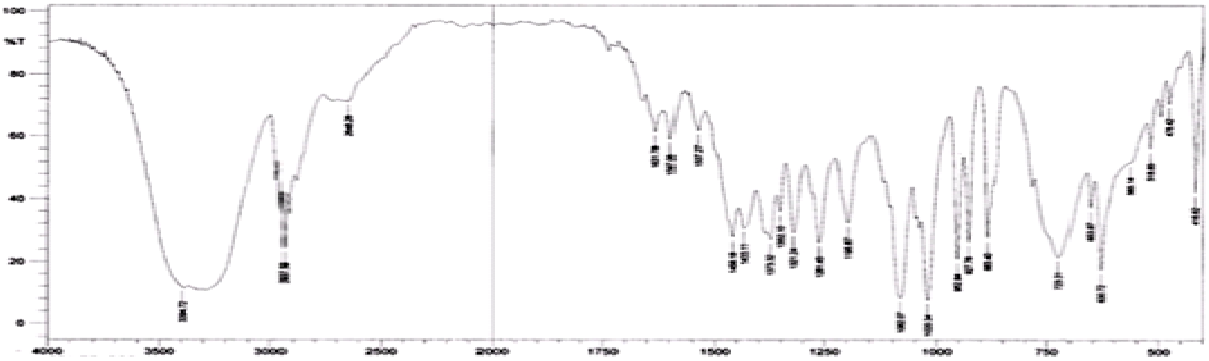
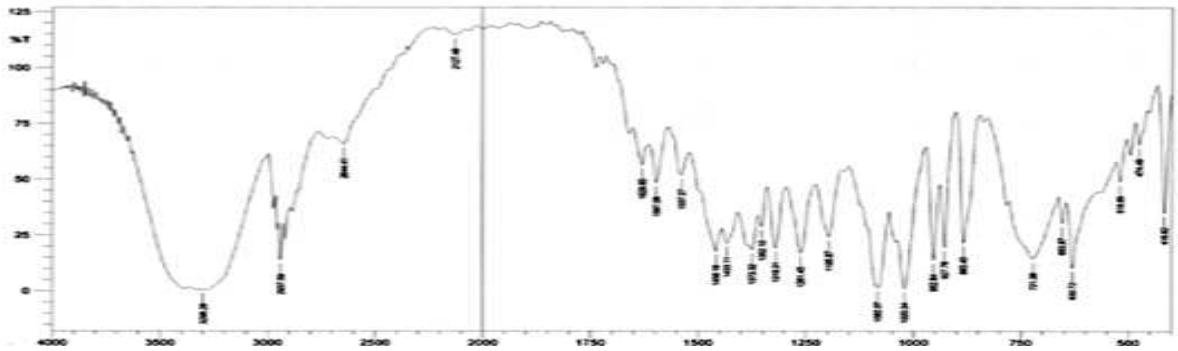


Figure 4: IR spectrum of drug along with HPMC showing prominent peaks



The IR spectra of drug in combination with polymers shows corresponding prominent peaks (**Figure 3& 4),** which indicates that there is no incompatibility between the drug and polymers used in the study.

Physical characteristics

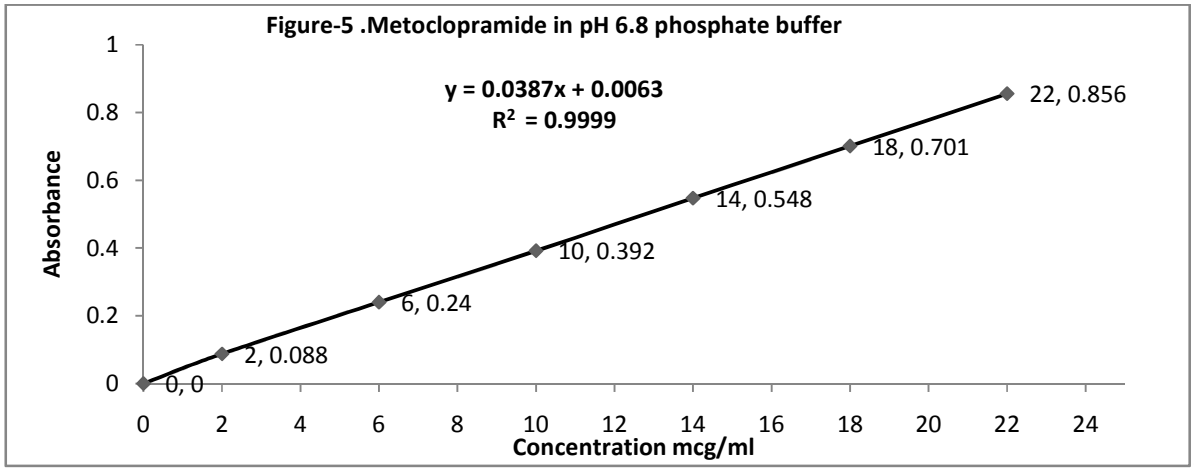
Characteristics such as homogecity, color, transparency and surface of the oral films were evaluated by visual inspection. F1 films were totally homogenous, absolutely transparent, colorless, both sides smooth. F2 films were Very homogenous, absolutely transparent, colorless, both sides smooth.

Uniformity of dosage units of the oral strips

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 F1 film preparations was found to be 99.40 ± 0.24% and 98.71±1.22 in F2 film preparations. 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^2 (3 x 2 cm).

Table-2: Standard graph of Metoclopramide in pH 6.6 phosphate buffer (λ max 273)

S.no	Concentration mcg/ml	Absorbance			Average	SEM
1	00	0.000	0.000	0.000	0.000	0.0000
2	2	0.089	0.088	0.87	0.088	0.0006
3	6	0.241	0.241	0.239	0.240	0.0007
4	10	0.391	0.390	0.395	0.392	0.0015
5	14	0.549	0.547	0.549	0.548	0.0007
6	18	0.702	0.700	0.700	0.701	0.0007
7	22	0.856	0.855	0.857	0.856	0.0006



Film mass

When manufacturing the oral films the film solutions were cast into sheets and then cut into smaller strips of 6 cm² (3 x 2 cm). Oral films were cut from different sheets and the variability between the sheets of the respective polymer was investigated. The nominal mass of film strip was calculated to be 57.29±0.29 for F1 films and 57.03±0.38 for F2 films. The nominal weight for each polymer was pre-determined and differs depending on film forming capacity and adherence to release liner.

Film thickness

In this study, strip thickness was measured by using Vernier calipers. As the formulations contained different polymers, hence the thickess was varied in the range of 0.206 to 0.211 mm.

Surface pH study

Considering the fact that acidic or alkaline pH may cause irritation to the mucosa of the oral cavity and influence the degree of hydration of polymers, the surface pH of the films was determined [22, 23]. The surface pH of the strips was observed to be 6.89±0.10 for F1 films and 6.83±0.09 F2 films. The surface pH of all the films was within the range of salivary pH. No significant difference was found in surface pH of different films.

Folding endurance

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding [22]. The folding endurance was measured manually, by folding the film repeatedly at a point till they broke. The breaking time was considered as the end point. Folding endurance was found to be highest for F1 films (199.33±2.16) and lowest for F2 films (191.16±3.06). The folding endurance values of the films were found to be optimum and therefore the films exhibited good physical and mechanical properties.

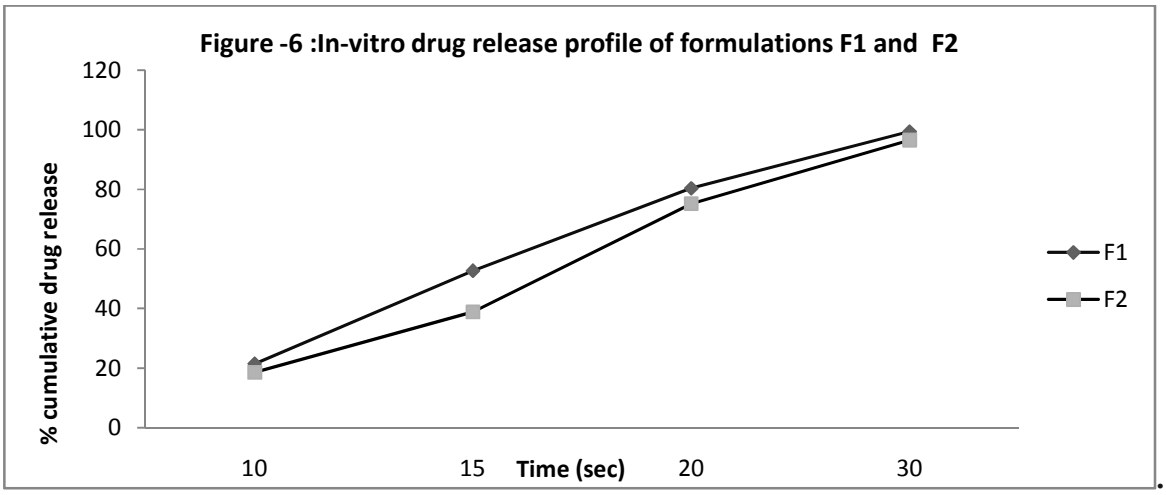
In vitro disintegration studies

All the fast dissolving films of each formulation were found disintegrate in less than 30 sec. F1 formulation found to gave minimum disintegration time (20.23±0.75) as compared F1 formulation (22.41±0.57).

In vitro Dissolution and release

The water-soluble hydrophilic polymers like HPMC E6 and SCMC 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 [24, 25].

In vitro dissolution and release studies of various formulations were performed using pH 6.8 phosphate buffer as dissolution medium and measuring drug concentration spectrophotometrically at 273 nm by using a calibration. The *in vitro* drug release profile from the films of formulae F1 and F2 in phosphate buffer pH 6.8 is shown in **[Figure - 6].** After 20 seconds time interval more than 75% drug was released from films. Drug release rate was very good with films containing HPMC E6 as a polymer.



CONCLUSION

Two water soluble polymers HPMC E6 and SCMC were used to produce an intraoral delivery system (Oral films) of Metoclopramide. Oral Films, loaded with 5 mg of Metoclopramide, were obtained with a casting-solvent evaporation technique. On the whole, our results demonstrated that the prepared polymeric films are promising candidates for release of Metoclopramide in the oral cavity within seconds: It was also concluded that formulation F1 (containing HPMC E6) and F2 (containing SCMC) showed good physical properties as well as promising drug release pattern. It may be concluded that the films containing 5 mg Metoclopramide in HPMC E6 (F1), show good physical properties and promising drug release than SCMC polymeric films (F2), thus seems to be a potential candidate for the development of oral film for effective therapeutic use. *In vivo* studies need to be designed and executed to substantiate further *in vitro* - *in vivo* correlation.

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