International Journal of Universal Pharmacy and Bio Sciences 8(4): July-August 2019

INTERNATIONAL JOURNAL OF UNIVERSAL PHARMACY AND BIO SCIENCES

IMPACT FACTOR 4.018*

ICV 6.16*

Pharmaceutical Sciences **Research Article……!!!**

DESIGN AND EVALUATION OF ORAL DISINTEGRATING FILMS OF RABEPRAZOLE SODIUM USING CO-PROCESSED POLYMERIC BLEND

Arpita Manjunath Gowdar*, Ashwini Rajendra, and Srinatha A.

Department of Pharmaceutics, National college of Pharmacy (NCP), Shimoga – 577201, Karnataka, India.

KEYWORDS:

Rabeprazole sodium, Oral disintegrating films, co-processed polymeric blend..

FOR CORRESPONDENCE:

Arpita Manjunath Gowdar*

ADDRESS:

Department of Pharmaceutics, National college of Pharmacy (NCP), Shimoga – 577201,
Karnataka, India.

ABSTRACT

Oral disintegrating films (ODF) of Rabeprazole sodium were formulated by solvent casting method using unit dose fabricated mould. Films were prepared with casting solution having Rabeprazole sodium as drug, Psyllium mucilage and HPMC K4M at the ration of 50:50, 60:40 and 40:60 as co-processed polymeric blend. It also contained sorbitol 70% LR as plasticizer, Sodium starch glycolate as super disintegrant and saccharin sodium as sweetening and stabilizing agent respectively. The drug and polymer compatibility were determined by FTIR. The results indicated no interaction had taken place. Formulation of single polymer was compared with co-processed polymeric blends. Coprocessed polymeric blends showed improved physicochemical and mechanical characteristics. The in vitro drug release study was performed in simulated salivary media (pH 6.8) for 30 min. All the formulations showed % drug release in the range of 80.27±0.13 % to 102.89±0.15 % within 20 min. The formulation F4 (60:40) showed 95.84±0.23 % of drug release in 15 min, MDT of 1.97 min and %DE of 120.73 % hence it was selected as best formulation. The F4 found to be stable during study period. The results indicated that co-processed polymeric blends showed very good mechanical, disintegration and dissolution property.

INTRODUCTION:

A fast disintegrating film or strip can be defined as a dosage form that aids water-dissolving polymer which helps the dosage form to hydrate quickly, adhere and dissolve when placed on the tongue or in the oral cavity to provide rapid local or systemic drug release. Drug release may be either quick or slow by varying the rate of dissolution of the films or, with formula modifications. Films will maintain the instant-dissolving aspect as well facilitating the absorption of drug throughout pharynx and oesophagus and allows for gastrointestinal absorption when it is swallowed [1].

Fast dissolving drug delivery system were first developed in the late 1970s an alternative to tablets, capsules and syrup for paediatric and geriatric patients who experience difficulties swallowing traditional oral dosage forms [2].

Gastric acid has got primary importance in digestion of food similarly the excessive secretion will decrease the pH causing inflammation and irritations on oesophagus along with burning sensation. So, use of acid suppresser or acid regulator is going to play an medicative prevention for an emergency situation. Hence H_2 blockers, antacids and proton pump inhibitors are used. Most commonly used proton pump inhibiters (PPIs) are prescribed for acid suppression in acute gastritis. They are also prescribed for the prophylaxis of stress ulcers and with NSAIDs [3].

Rabeprazole sodium being salt form very soluble in water, rapidly degrades in acid media, maintains gastric pH >4 for 15-25 hours by protein binding (96.3 %)[4]. The mucin restoration capacity of Rabeprazole sodium provides clinical benefit of protection of the upper alimentary tract from NSAID related mucosal injury, which makes it suitable for preparation of ODFs[5] .

The choice of film-forming polymer is the first step in the development of oral disintegrating film. Biopolymers like polysaccharides are most preferred to formulate oral films. The mucilage derived from the seeds of *Plantago ovata* (family Plantaginaceae) was investigated for film forming ability, rate of disintegration and % drug release. The extracted mucilage was combined with laboratory grade polymers with poor film forming ability, to co-process as newer polymeric blend to achieve faster disintegrating properties. HPMC K4M are having very poor film forming ability[6]. Such polymers were blended with polymer of higher molecular weight to achieve proper mechanical characteristics of film.

Co-processed polymer was made by combining 2 or more excipients in an optimized ratio or method to provide superior synergistic properties and improves the functionality as well as masking the undesirable properties of individual excipients[7].

Conventional methods of preparing ODFs using petri plates have limitations such as drug uniformity, viscosity alterations, stickiness etc... In this work fabricated silicone mould were used to form a unit dose ODF (Figure 1),

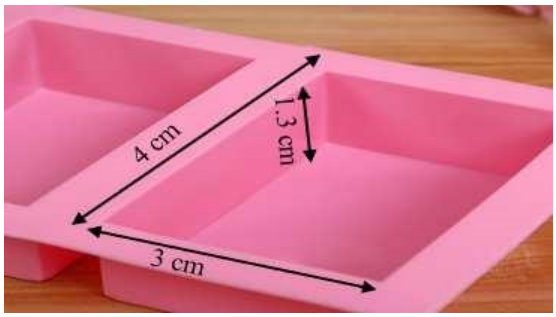

Figure 1: Silicon mould

MATERIALS AND METHODS:

Materials:

Standard drug Rabeprazole sodium was obtained as gift sample from Micro labs, Bangalore, India.Psyllium Seeds was purchased from Local market. HPMC K4M was procured from Colorcon Asia Pvt Ltd, Goa, India. Sorbitol 70% LR, Sodium starch glycolate and Sodium saccharin were procured from SD fine chemicals, Mumbai, India. All the other chemical reagents were of analytical grade.

Extraction of mucilage powder from psyllium seeds:

Plantago ovata seeds of good quality were segregated foreign particles and soaked with sufficient distilled water for about 2 hours. Then the mucilage was extruded by heating for 10 min in hot water bath at temperature of 80°C. The extruded mucilage was collected by squeezing through muslin cloth and dried in hot air oven at a temperature less than 50°C until gets dried completely. Then powdered using motor and pestle. The fines were collected by passing through sieve # 80[8].

Preparation of drug loaded ODFs:

Films were prepared by solvent casting method. Initially different concentration of extracted polymers and plasticizers were selected and optimized to get mechanically stable film as given in Table 1. Polymer were weighed accurately for unit dose, and dissolved in water (solvent) and heated in water bath to get gel like mass. Uniform dispersion of polymeric solution with plasticizer and drug is achieved by stirring constantly with a glass rod. Then the obtained solution casted in to a silicon mould of accurate surface area and allowed to evaporate solvents in hot air oven with levelled surfaces maintained at 60°C till a flexible film was formed. The films of respective compositions were fabricated as given in the Table 2. The Formulated films were packed in aluminum foil and stored in air tight desiccator till further use.

Calibration curve of Rabeprazole sodium in Simulated salivary media

The aliquots 3-30µg/ml was prepared in Simulated Salivary media (pH 6.8)[9]. The absorbance of these solutions was determined by UV spectrophotometer at 283nm and calibration curve was plotted. The study was performed in triplicate and result was expressed as mean ± SD.

Physicochemical and mechanical properties of the ODFs:

Physicochemical evaluation such as average moisture content retained, % moisture lost on drying, Thickness of the film, Content uniformity of the film, and surface pH of the film were performed for the ODFs as per the standard procedure and the results are shown in (Table 3) mean± SD values (n=3)[10]. The average moisture content and % moisture lost on drying were determined gravimetrically. The thickness of each film was measured using Dials meter (Mitutoyo, Japan). Mechanical properties such as tensile strength and percentage elongation were performed with Texture analyzer (Universal texture machine Hounsfield)and in vitro disintegration of films were determined by petri plate method and the time of breaking was noted for every film in petri plate containing 20 ml of simulated salivary media (pH6.8), the results are shown in Table 4.

In vitro drug release studies of the ODFs:

The in vitro drug dissolution study was performed using eight station dissolution test apparatus (USP) TDT-08L (Electrolab, Mumbai, India), with a paddle speed of 50 rpm. Dissolution medium consisted of 900 ml of simulated salivary media (pH 6.8) maintained at 37± 0.5 ºC. At a predetermined time, intervals an aliquot was withdrawn and replenished with fresh medium. Amount of drug in each aliquot was assayed on a UV-Spectrophotometer (UV-1601, Shimadzu, Japan) at 283 nm using simulated salivary media (pH 6.8) as blank. All the trials were conducted in triplicate and the average (± S.D) reading was noted.

Model independent parameter:

The invitro drug release data of the formulations were analysed for Dissolution efficiency (DE) and Mean dissolution time (MDT) using Microsoft excel with respective formula

$$DE\ \% = \frac{\int_0^t y\ dt}{y_{100}} t \times 100$$

Where, y is the drug percent dissolved at time t.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Where *'i'* is the dissolution sample number, *'n'* is the number of dissolution sample time, *'t_{mid}'* is the time at the midpoint between '*i'* and *'i-1'*, and *'ΔM'* is the amount of drug dissolved between *'i'* and *'i1'*[11].

Drug and excipients compatibility study using Fourier Transform Infrared Spectroscopy (FTIR): The characteristic peaks of the pure drug and formulations were obtained by scanning in the range of 4000-400-1 by using FTIR-Bruker, Tensor, Europe.

Accelerated stability studies:

Accelerated (40ºc / 75% RH) stability study was carried out as per international guidelines at time intervals 2, 4 and 6 weeks using programmable stability chamber. Films were evaluated for change in physical parameter, drug release and drug content.

Table 1: Film forming ability of *Psyllium* mucilage powder along with different plasticizer.

Formulations	Composition	Film forming ability
P1	5 mL S* + 0.3 mL Glycerine	Oily texture film ruptured with irregular surface
P2	5 mL S* + 0.3 mL sorbitol 70% LR	Glossy and perfect texture and flexible
P3	5 mL S* + 0.3 mL propylene glycol	Brittle and irregular texture
P4	5 mL S* + 0.3 mL poly ethylene glycol 200 LR	Sticky mass no film texture

* S- Aqueous solution of 1% w/v mucilage powder pre heated to jellifies.

Table 2: Composition of rabeprazole sodium ODFs along with formulation code.

Ingredients	F1	F2	F3 (50:50)	F4 (60:40)	F5 (40:60)
Rabeprazole sodium (mg)	20	20	20	20	20
Mucilage polymer (%w/v)	1	-	1	1	1
HPMC K4M (%w/v)	-	1	1	1	1
Sorbitol 70% LR[a](ml)	0.3	0.3	0.3	0.3	0.3
Saccharine sodium[b](%w/w)	1	1	1	1	1
Sodium starch glycolate[c] (%w/w)	6	6	6	6	6
Distilled water[d](ml)	5	5	5	5	5

a) Sorbitol 70% LR is used as plasticizer.

b) Saccharin sodium as sweetening as well as stabilizing agent.

c) Sodium starch glycolate used as super disintegrant.

d) Distilled water is common solvent to implement a solvent casting.

Table 3: Physicochemical properties of the ODFs.

Formulation	Average moisture retained (gm^{-2}) ± SD	Moisture lost on drying (%) ± SD	Thickness (mm) ± SD	Content uniformity (%) ± SD	pH ± SD
F1	2.41±0.05	95.00±0.15	0.34±0.60	97.99±0.15	7.31±0.12
F2	2.25±0.23	92.59±0.05	0.44±0.04	108.39±0.01	7.39±0.01
F3	2.34±0.08	92.91±0.05	0.42±0.02	92.33±0.07	7.22±0.25
F4	2.45±0.06	96.76±0.02	0.38±0.03	103.83±0.01	7.28±0.01
F5	2.23±0.12	96.61±0.03	0.32±0.07	107.84±0.08	7.30±0.32

Values are mean ± SD, n=3

Table 4: Mechanical Property and in vitro disintegration time of the ODFs.

Formulation	Disintegration time (sec)± SD	Tensile strength (Kg/mm^2) ± SD	Elongation at break (%mm^{-2})± SD
F1	119.66±0.23	0.051±0.30	41.36±0.05
F2	102.30±0.06	0.026±0.12	27.06±0.12
F3	75.30±0.03	0.063±0.06	36.16±0.07
F4	68.23±0.06	0.055±0.12	35.06±0.15
F5	70.35±0.04	0.051±0.05	33.73±0.01

Values are mean ± SD, n=3

Table 5: Model independent parameters of the ODFs.

Formulation	MDT (min)	% DE15min
F1	3.07	113.06
F2	3.09	113.37
F3	2.80	114.87
F4	1.97	120.73
F5	2.48	116.85

Table 6: The FTIR peaks of pure drug and selected formulation F4

Functional group	Wave number (cm^{-1})	
	Pure rabeprazole sodium	F4
Aromatic C-H (str)	3107.54	3102.97
C-H (str) of CH_3	3014.72	2941.74
C-H (str) of CH_2	2855.99	2841.19
N-H (str)	3320.16	3299.13
C-N (str of pyrrolidone)	1550.48	1530.57
S=O	1215.18	1193.39
C-O (str)	965.85	1050.72
C- S (str)	710.57	701.41

Table 7: Accelerated stability studies of physical parameters and content uniformity tests for the formulation F4.

Evaluation parameter	F4			
	0 week	2 weeks	4 weeks	6 weeks
Moisture content (gm^{-2})	2.27	2.33	2.83	2.68
Thickness (mm)	0.37	0.27	0.27	0.28
pH	7.29	7.27	7.24	7.24
Content uniformity (%)	95.62	95.24	95.05	94.48

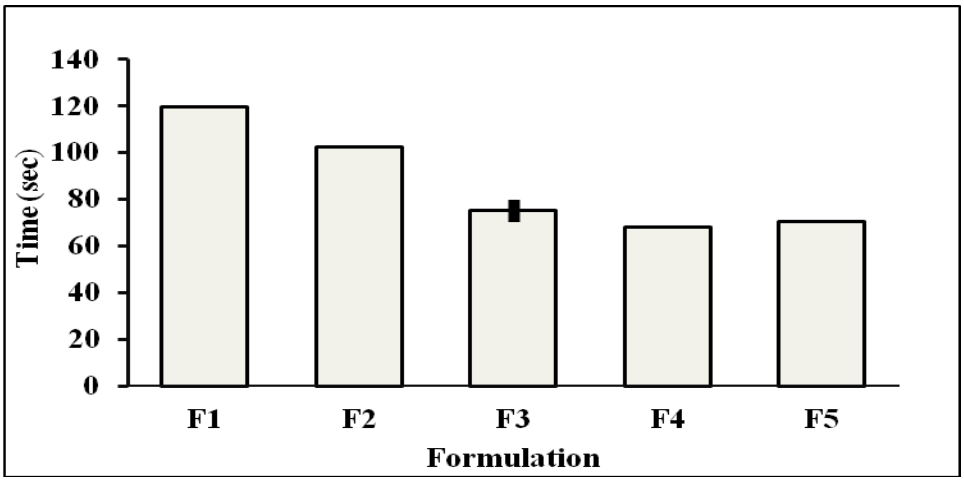

Figure 2: Comparison of in vitro disintegration times of different ODFs:

 International Standard Serial Number (ISSN): 2319-8141

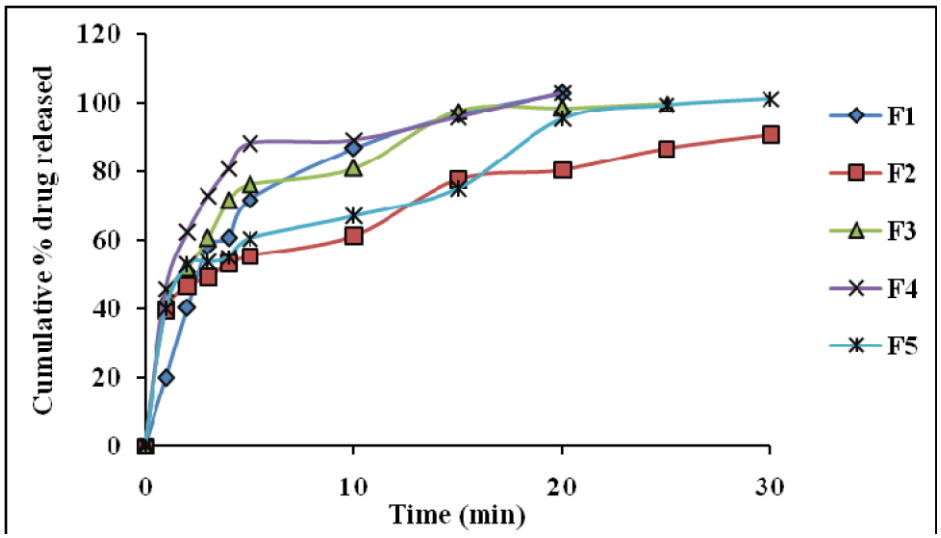

Figure 3: Invitro dissolution profiles of the ODFs.

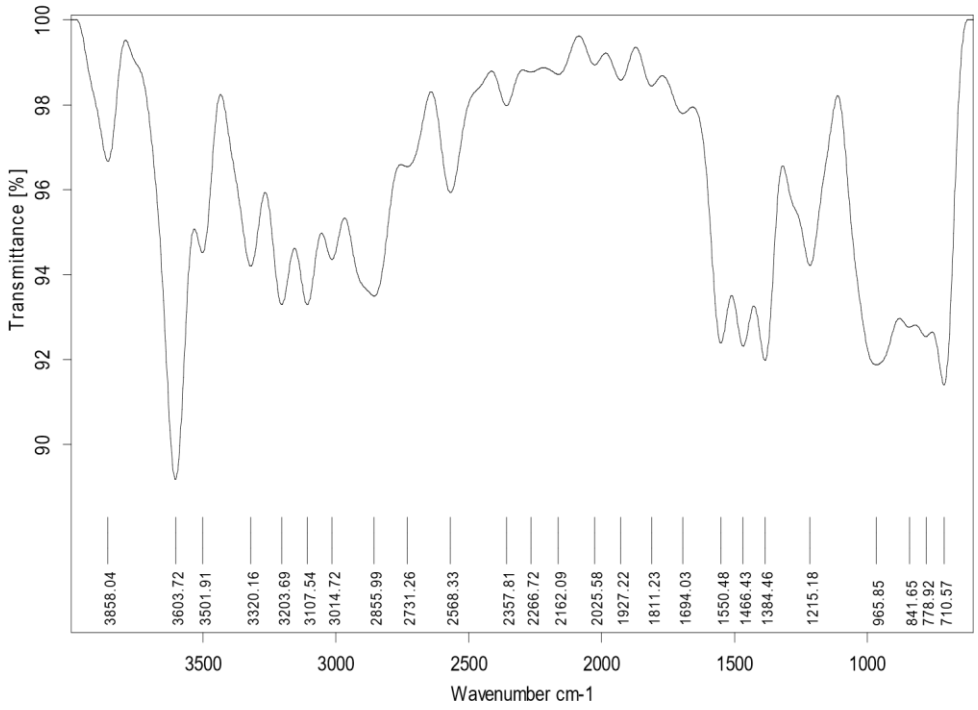

Figure 4: FTIR spectrum of pure Rabeprazole sodium.

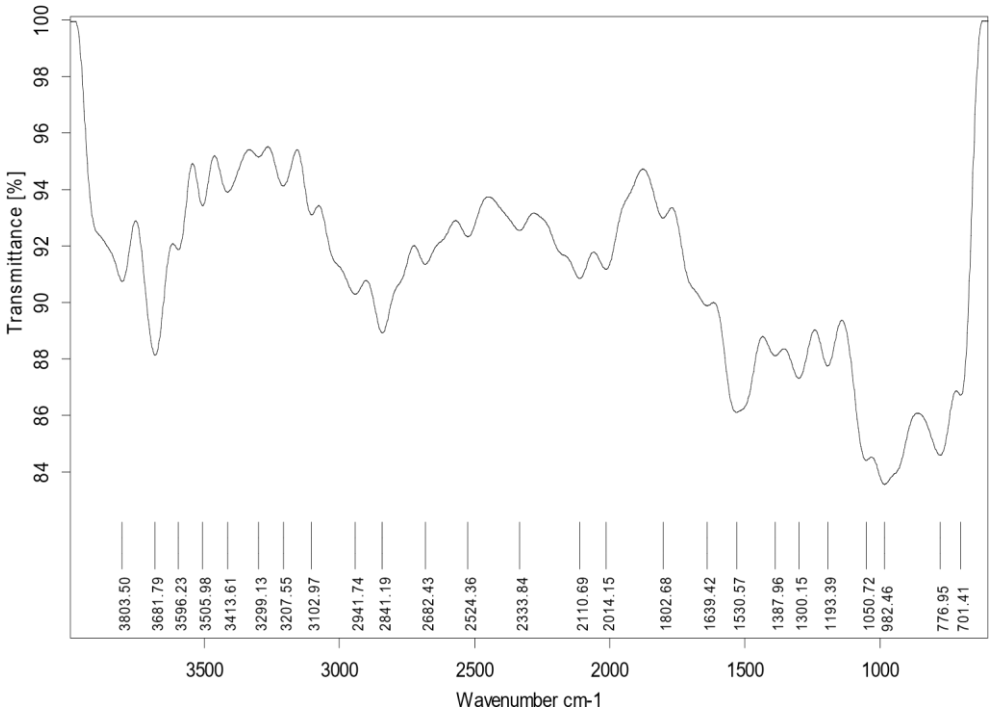

Figure 5: FTIR spectrum of the Formulation F4.

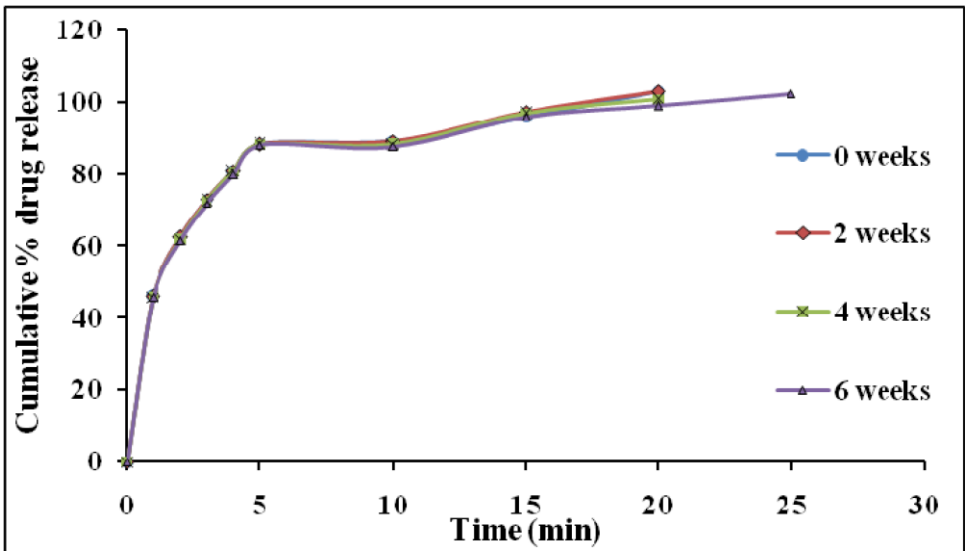

Figure 6: Comparative graph for in vitro dissolution study of the formulation F4 in 0, 2, 4 and 6 weeks of stability study

RESULTS AND DISCUSSION:

In this study the oral disintegrating films of Rabeprazole were prepared by psyllium mucilage in combination with HPMC K4M as co-processed polymeric blend, using unit dose solvent casting technique. The calibration curve of Rabeprazole sodium was found to be linear and Obeyed beers-lamberts law with regression value of 0.9997.

Film forming ability of the psyllium mucilage powder:

Extracted mucilage powder was evaluated for phytochemical constituents and physicochemical characteristics as described by[12]. The extracted mucilage powder showed satisfactory properties. The mucilage showed satisfactory film forming property with Sorbitol than other plasticizers.

Physicochemical and mechanical properties of the ODFs:

Unit dose approach for the preparation of films helped to get uniform and fair physicochemical and mechanical properties. Formulation procedures involved fewer processing steps, no major drug loss was observed during the preparation of the films. Minimal moisture retention is necessary for film to peel easily. The moisture content should not be very high as the films will become stickier and adhere to the mould. Surface pH was found to be neutral and were compatible to oral mucosa. Sodium starch glycolate at 6% w/w concentration showed ideal properties to have fast disintegration of the film. The co-processed polymeric films showed faster disintegration and good texture than the individual polymeric films.

In vitro dissolution studies of the ODFs

The formulations F1(psyllium mucilage), F2 (HPMC K4M), F3-(50:50), F4-(60:40) and F5-(40:60) are showing 102.77±0.08 %, 80.27±0.13 %, 98.32±0.06 %, 102.89±0.15 % and 95.38±0.23 % cumulative % drug release in 20min respectively. Drug release was found to be highest for formulation F4. The release rate was decreased as the concentration of HPMC K4M increased.

Model independent evaluation of the ODFs:

The MDT and DE values of the all the films found to be satisfactory. Among all formulations, formulation F4 was selected as best formulation with disintegration time 68.23±0.06 sec, MDT 1.97 min and DE_{15min}120.73 %. The results showed that co-processed formulations were found to be good approach as disintegrating oral films.

Compatibility study (FTIR):

The spectra of Rabeprazole sodium showed the peak assigned to C-H stretching of aromatic ring at 3107.54cm^{-1}, C-H stretching of CH_3 at 3014.72cm^{-1}, C-H stretching of CH_2 at 2844.99cm^{-1}, N-H stretching at 3320.16 cm^{-1}, C-N stretching of pyrrolidone at 1550.48cm^{-1}, S=O stretching at 1215.18cm^{-1}, C-O stretching at 965.85cm^{-1} and C-S stretching at 710.57 cm^{-1} . The characteristic peaks of pure drug attributed to the functional group, are found in FTIR spectra of formulation F4 (Figure 4 & 5). This indicated the drug and polymers were compatible as no interaction had taken place.

Accelerated stability study:

Accelerated stability study on selected formulations F4 was performed at 40°C / 75% RH for 6 weeks. The results of physical changes and drug content were shown in Table 7. The comparative graph of drug release

pattern during above mention periods were shown in Figure 6. The result was found to be stable within period of accelerated condition. As the formulations are sensitive to atmospheric condition, so has to be desiccated with proper packages.

CONCLUSION:

From the results, it can be concluded that the oral disintegrating films of Rabeprazole sodium was formulated successfully and achieved enhanced disintegration and dissolution profile using coprocessed polymeric blend. With the aid of unit dose solvent evaporation method ODFs showed desire physicochemical and mechanical characteristics.

REFERENCES:

1. Reddy D, Pillay V, Choonara YE, Du Toit C. Rapidly disintegrating Oramucosal drug delivery. Pharm Dev Technol. 2009;14(6):588–601.
2. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral film an innovative drug delivery system and dosage form. Int. J. Chem. Tech. Res. 2010;2: 576-83.
3. Padhy B, Singh H, Gupta YK. Attitude and Knowledge of Indian Emergency Care Residents towards Use of Proton Pump Inhibitors. Int Sch Res Notices. 2014:1-6.
4. https://www.drugbank.ca/drugs/DB01129 accessed on 12/4/19.
5. Jaworski T et al., Restorative Impact of Rabeprazole on GastricMucus and Mucin Production Impairment During Naproxen Administration: Its Potential Clinical Significance.Digestive Diseases and Sciences. 2005;2(50):357-65.
6. Kulkarni AS, Deokule HA, Mane MS and Ghadge DM. Exploration of different polymers for use in the formulation of oral fast dissolving strips. Int J Cur Pharm Res. 2010; 2(1):33–35.
7. Gandhi PP, Mundada AS.Formulation and Evaluation of Co-processed Excipient for Mouth Dissolving Formulation. Int J Drug Dev & Res.2016; 8:030-035.
8. Rajamanickam D. Furtado S, Srinivasan B, AbrahamS,VeerabhadraiahB,MadhavanV.Isabgol mucilage as a potential natural suspending agent. Int J Res Ayurveda Pharm.2010;1(2): 543-48.
9. Margareth C, Raimar L, Almukain. Simulated biological fluids with possible application in dissolution testing. Dissolution Technol. 2011:15-28.
10. Prabhu P et al, Formulation and evaluation of fast dissolving films of levocetirizine di hydrochloride. Int J Pharm Investing. 2011;1: 99–104.
11. Costa P, Lobo J. Modeling and Comparison of dissolution profiles: A review. Eur J Pharm Sci. 2001; 13:123-33.
12. Geetha KP, Gowda S, Kulkarni GT. Microwave assisted fast extraction of mucilages and pectins. Indian J Pharm Educ Res. 2009;43: 260-265.