WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 3, 732-743. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION STUDIES OF ENTERIC COATED TABLET CONTAINING NON-STEROIDAL ANTI-INFLAMMATORY DICLOFENAC SODIUM

Dr. S. Chandra*, B. Nandhini, D. Ezhilarasi, S. Kavi bharathi, S. Sangeetha, A. Sheikalish

India.

Article Received on
03 Jan. 2020,

Revised on 23 Jan. 2020,
Accepted on 14 Feb. 2020

DOI: 10.20959/wjpr20203-16758

***Corresponding Author**
Dr. S. Chandra
India.

ABSTRACT

In the present study, an attempt has been made to formulate and evaluate enteric coated tablets of Diclofenac sodium using two different enteric polymers that will only dissolve in the small intestine, such as cellulose acetate phthalate and methacrylic acid ethyl acrylate copolymer to reduce the gastrointestinal tract side effects. Preformulation studies were performed to analyze the characteristics of Diclofenac sodium. Drug and excipients were confirmed to be standard without any incompatibility by Drug Excipients Compatibility study. Four formulations of core tablets were prepared by wet granulation method and good flow properties were observed. All the physical parameters like appearance, weight variation, thickness, hardness, friability and disintegration time were found to be within the limits for F4 formulation and selected for further enteric coating. Enteric coating was optimized using two different enteric polymers in different concentrations to achieve various percentage weight gains. *In vitro* analysis, Assay and Related Substances test were carried out. The *in vitro* release results showed that the enteric coated tablets were capable of restricting release in acidic media. The optimized formulation was capable of releasing the drug in pH 6.8 in a same manner as marketed formulation of Diclofenac sodium.

KEYWORDS: Diclofenac sodium, Enteric coating, Delayed release, cellulose acetate phthalate, methacrylic acid ethyl acrylate copolymer.

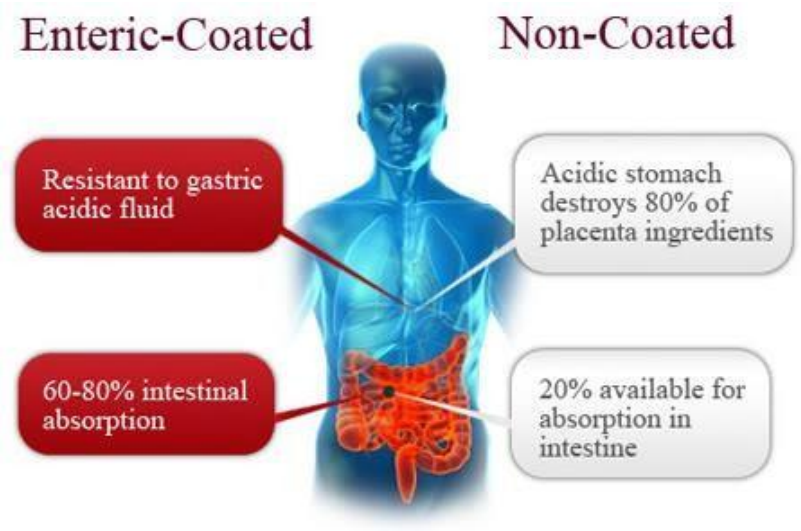
INTRODUCTION

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID), which is very effective in the management of pain, inflammation and stiffness caused by many conditions such as osteoarthritis, rheumatoid arthritis, abdominal cramps associated with menstruation, and ankylosing spondylitis. Diclofenac is categorized as a nonselective COX inhibitor with potency substantially greater than that of indomethacin and naproxen. In addition, diclofenac appears to reduce intracellular concentrations of free arachidonate in leukocytes, perhaps by altering release or uptake of the fatty acid.

In humans, diclofenac is rapidly and completely absorbed after oral administration, and the peak plasma concentration is reached within 2-3 hours. There is a substantial first pass effect, and approximately 50% of the drug is available systemically. In humans, diclofenac extensively binds to plasma proteins (99%) and its plasma half-life ranges from 1 to 2 hours. It is metabolized in the liver by a cytochrome P450 isozyme of CYP2C subfamily to 4-hydroxydiclofenac, the principal metabolite and other hydroxylated forms. After glucuronidation and sulfation, the metabolites are excreted in urine (65%) and bile (35%).

Enteric Coated tablets

A tablet that has a special outer covering designed to dissolve in the small intestine. Once the enteric-coating is dissolved the tablet disintegrates and the active ingredient can be absorbed by the patient. An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The word “enteric” indicates small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine. The enteric coated polymers remain unionize at low pH, and therefore remain insoluble. But as the pH increases in the GIT, the acidic functional groups are capable of ionization and the polymer swells or becomes soluble in the intestinal fluid. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac and plant fibers.



Enteric coated Vs Non-coated Tablets.

Composition of Enteric Coated Tablet

The Enteric coated formulation usually contains the following component.

Polymers

Polymers are substance containing a large number of structural units joined by the same type of linkage. These substances often form into a chain-like structure starch, cellulose, and rubber all possess, polymeric properties. With an acid-resistant property, enteric coating polymers generally possess free carboxylic acid groups on the polymer backbone. They are insoluble in acidic media but become deprotonated and dissolved in basic media at pH nearly neutral values (pH>5).

Plasticizer

Success of enteric coating efficiency mostly relies on the addition of plasticizers. Plasticizers are a group of auxiliary components that improve elasticity of the polymeric film. A wide range of plasticizers are available to the formulator such as phthalate esters, phosphate esters, other esters like citrates, stearates, sebacate, oleate, adipate etc. oils, glycerol, glycols etc. The type of plasticizer should be selected carefully as it influences the film brittleness, compatibility with the coating substrates and product stability.

Solvent

Aqueous and hydro alcoholic solutions are used to dissolve or disperse the polymers and other additives and convey them to substrate surface.

Additives

The properties and composition of other components of the film coating formulation also need to be considered and optimized to get the most desired effects without affecting the quality of the film.

Pigments/Colorant

The commonly used colorants in coating are water soluble dyes. However, the overall color effect of these dyes depend on the dye concentration at a particular point, thickness of film at that point and the residual moisture content in the film at that point.

Opacifier

The opacity of the film depends on the difference between the refractive index of the polymer and other components of the coating formulation. The lake colors used in enteric coating has refractive index similar to that of various polymers, thus the opacity of lake colors is very poor. eg Titanium Oxide.

Anti-tacking agent

The most commonly used anti- tacking agent is Talc, which is used in higher concentration tends to settle down from the coating suspension, thus constant stirring of solution is recommended during the coating process.

Study rationale

- Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID), which is very effective in the management of pain, inflammation and stiffness caused by many conditions such as osteoarthritis, rheumatoid arthritis, abdominal cramps associated with menstruation, and ankylosing spondylitis.
- Varied clinical responses in products of the same drug are also dependent on the level of in-process quality control observed by the manufacturers from the point of raw material purchase to when the tablets are packaged and distributed.

MATERIALS AND METHODS

Diclofenac was obtained as gift sample was Amoli organics Pvt Ltd, India, Lactose monohydrate, Maize starch, Crospovidone XL-10, Micro crystalline cellulose, Povidone K30, Colloidol silicon dioxide, Magnesium stearate, Cellulose acetate phthalate, Titanium Dioxide, Kollicoat MAE 100P, Triethyl citrate, Talc.

METHODOLOGY

Preformulation studies

Preformulation studies are designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical and analytical investigation in support of promising experimental formulations.

Formulation of enteric coated tablets

Delayed release tablets of Diclofenac sodium (75 mg) were prepared through wet granulation method as per the composition shown in Table:

Compositions of different core formulations.

Ingredients	**F1**	**F2**	**F3**	**F4**
	mg/tab			
Intragranular part				
Diclofenac sodium	75	75	75	75
Lactose monohydrate	24	21.6	14.63	14.63
Maize Starch	16.2	16.2	9.46	9.46
Crospovidone	-	1.2	-	-
MCC PH 101	-	-	14.54	14.54
Binder				
Povidone K30	3	3.6	5.4	5.4
Isopropyl alcohol	Qs	Qs	Qs	Qs
Lubrication				
Colloidal Silicon Dioxide	0.6	1.2	-	-
Magnesium Stearate	1.2	1.2	0.97	0.97
Tota	**120**	**120**	**120**	**120**

EVALUATION OF PRECOMPRESSION PARAMETERS

Bulk density

Accurately weighed 10g of final blend was transferred into 50mL graduated cylinder. Carefully the granules were leveled without compacting and the unsettled apparent volume was noted.

$$\text{Bulk density} = \frac{\textbf{Weight of the granules}}{\textbf{Bulk volume of the granules}}$$

Tapped density

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample.

$$\text{Tapped density} = \frac{\text{Weight of the granules}}{\text{Tapped volume of the granules}}$$

Compressibility index

The propensity of a powder to be compressed and interparticulate interactions is measured by compressibility index. Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

$$\textbf{Compressibility index (\%)} = \frac{\textbf{(Tapped density – Bulk density) x 100}}{\textbf{Tapped density}}$$

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. Hausner's ratio was calculated from the bulk and tapped density using the following formula,

$$\textbf{Hausner's ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}}$$

Evaluation of post compression parameters

The compressed tablets were evaluated for the following parameters.

Physical appearance

The formulated tablets were inspected for color, shape, dimension, smoothness, absence of cracks, chips, and other undesirable characteristics.

Weight variation

Weight variation test is performed to check that the manufactured tablets have a uniform weight.

Procedure: Twenty tablets were weighed individually and average weight was calculated, and the individual weight was compared with average weight. The difference in weight was determined and % variation was calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage given in the table.

Percentage deviation of tablets

Average weight of tablet (mg)	Percentage deviation
80 or less	±10.0
80 – 250	±7.5
More than 250	±5.0

Thickness

Once the tablet size and shape have been established, tablet thickness remains the only overall dimensional variable. Thickness should be controlled within 5% or less of an established standard value. Excessive variation in tablet thickness can result in problems with packaging as well as consumer acceptance. Variation in tablet thickness can also indicate force.

Hardness

Tablet hardness and strength are the essentials to see that the tablet can withstand the shock and stress during manufacturing, packing and transportation, and while handled by the patient. It may be especially important to monitor the tablet hardness for sustained release drug products or other products that possess real or potential bioavailability problems or sensitive to variations in drug release profile. Hardness should be controlled within 5% or less of an established standard value.

Friability

Friability is the measure of a tablet's ability to withstand both shock and abrasio n without crumbling during the handling of manufacturing, packing, shipping and consumer use. Tablets that tend to powder, chip, and fragment when handled lack elegance, and hence, consumer acceptance.

$$\textbf{Percentage Friability} = \frac{\textbf{W1} - \textbf{W2}}{\textbf{W1} \times \textbf{100}}$$

W1 = Weight of tablets before testing. W2 = Weight of tablets after testing.

Disintegration test

This test determines whether the enteric coated tablet disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions. Disintegration is defined as that state in which no residue of the tablet under test remains on the screen of the apparatus. The tablets pass the test if all the six tablets have disintegrated.

RESULTS AND DISCUSSION

Evaluation of pre compression parameters

Precompression parameters of all core formulations

Formulation code	Bulk density (g/mL)	Tapped density (g/mL)	Compressibility index (%)	Hausner's ratio
F1	0.521±0.2	0.905±0.2	42.4±0.3	1.74±0.1
F2	0.545±0.3	0.857±0.3	36.4±0.3	1.57±0.2
F3	0.377±0.2	0.431±0.1	12.5±0.2	1.14±0.1
F4	0.384±0.2	0.444±0.2	13.6±0.2	1.16±0.2

Evaluation of post compression parameters

Physical characteristics of all core formulations

Formulation code	Average weight** (mg)	Thickness* (mm)		Hardness* (N)		Friability (%)*
		min	max	min	max	
F1	120.6±1.2	3.08± 0.3	3.18± 0.3	48± 0.4	56± 0.2	0.27±0.02
F2	121.4±1.3	3.09± 0.4	3.18± 0.2	43± 0.5	60± 0.3	0.12±0.03
F3	121.2±0.6	3.22± 0.5	3.34± 0.2	101± 0.1	112± 0.3	0.09±0.02
F4	121.3±0.8	2.99± 0.8	3.20± 0.2	102± 0.2	119± 0.4	0.08±0.01

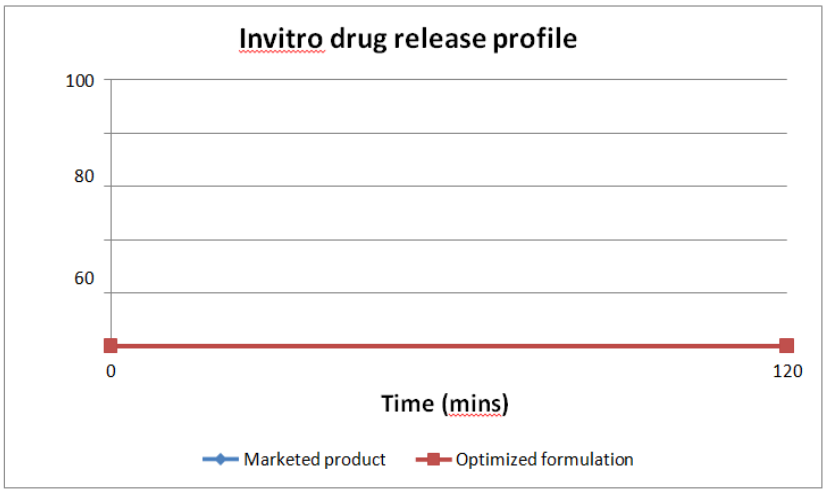
* All the values are expressed as mean ± SD; n=3.

** All the values are expressed as mean ± SD; n=20.

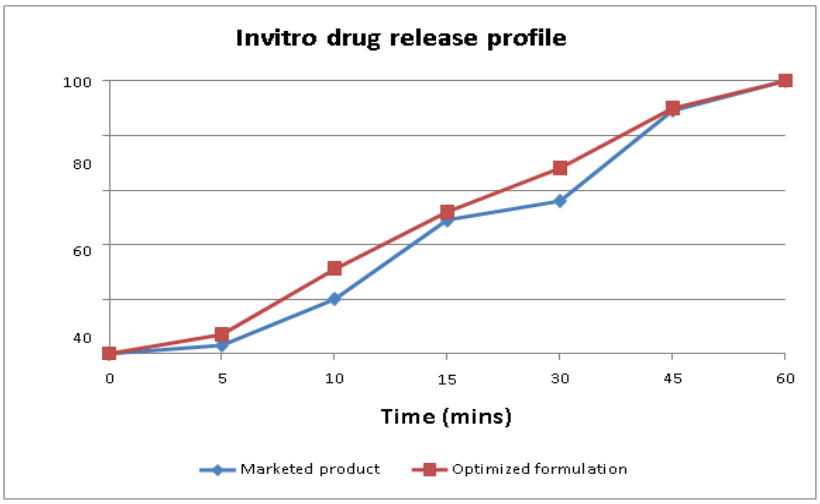
DISINTEGRATION TIME

Disintegration time of all coating formulations in both acidic and basic medium

Formulation code	% build up	Disintegration time*	
		0.1N HCl	Phosphate buffer pH 6.8
C1	12	No cracks	30min 03sec to 33min 11sec
	15	No cracks	31min 09sec to 33min 04sec
C2	8	No cracks	25min 05sec to 29min 30sec
	10	No cracks	29min 15sec to 32min 15sec
C3	4	No cracks	19min 20sec to 20min 31sec
	8	No cracks	23min 59sec to 24min 30sec
C4	8	No cracks	23min 49sec to 24min 21sec
	9	No cracks	23min 10sec to 23min 49sec

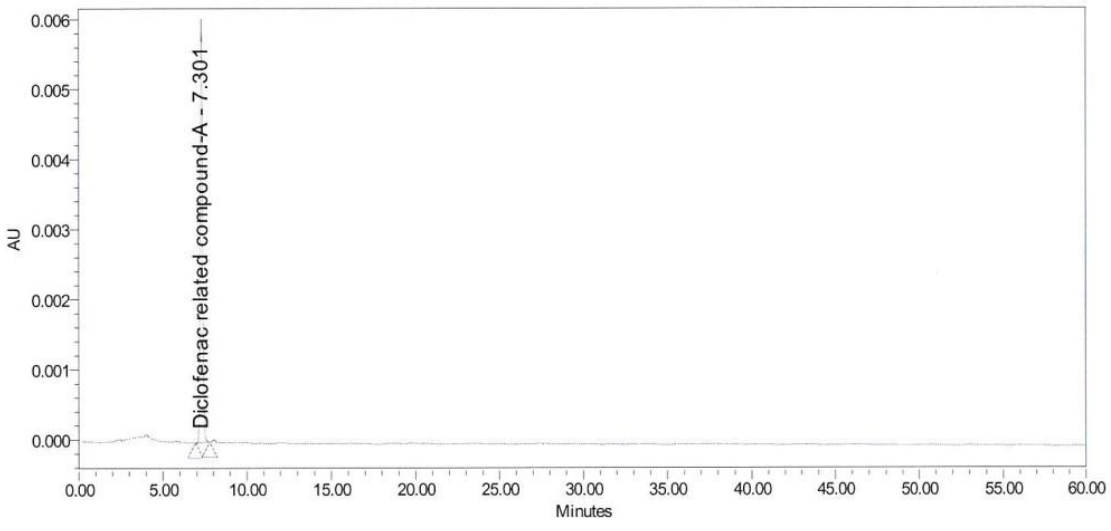


***In vitro* drug release profile in acidic medium (0.1N HCl)**

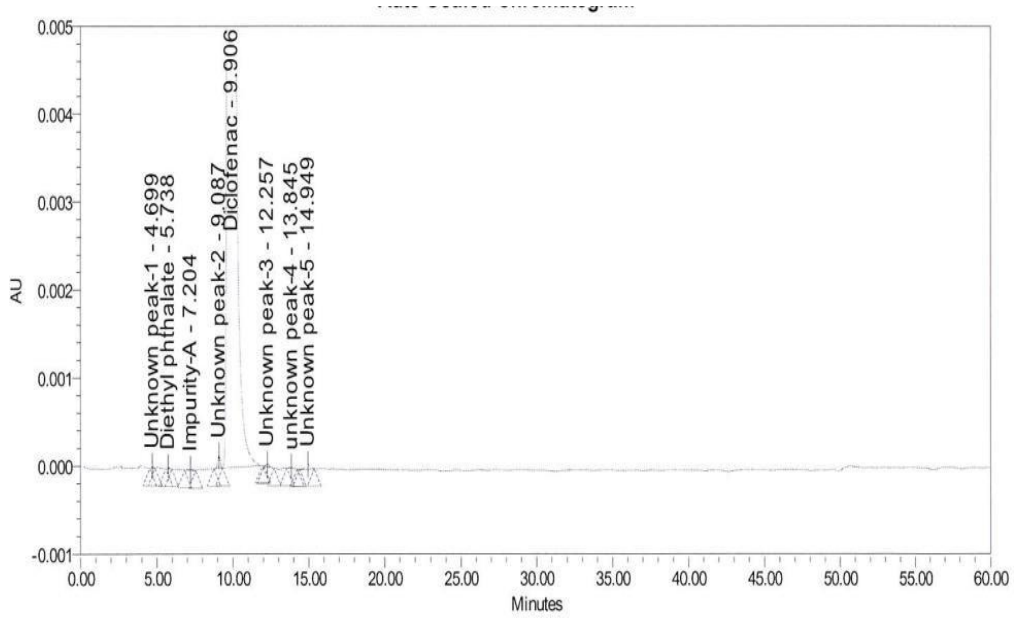


***In vitro* drug release profile in basic medium (Phosphate buffer pH 6.8)**

Related substance (By HPLC)



The chromatogram of Diclofenac sodium RS (Standard)



The chromatogram of Diclofenac sodium RS (Sample O1)

CONCLUSION

Formulation and evaluation of enteric coated tablets of Diclofenac sodium was successfully carried out by performing the preformulation studies, formulation of Diclofenac sodium enteric coated tablets, evaluation parameters and *In vitro* drug release studies.

- The preformulation studies of API and DEC studies showed that the drug is compatible with the excipients used in the formulation.
- The prepared powder blend results indicated that it has good flow property for wet granulation method.
- All the physical parameters of prepared tablets were found to be within the pharmacopoeial limits in optimized formulation which was coated with methacrylic acid ethyl acrylate copolymer.
- *In vitro* drug release study carried out for F4 shows optimized formulation 100% drug release at 60mins.
- Comparative *In vitro* dissolution study of optimized formulation showed similar drug release to the marketed product.
- From all the above observations it was concluded that the optimized formulation was better one compared to the other formulations.

REFERENCES

1. Savaser A *et al.*, prepared and evaluated the *In vitro* dissolution of sustained release tablet formulations of diclofenac sodium. The effects of formulation variables on the release profile of diclofenac sodium (DS) from hydroxypropylmethyl cellulose (HPMC) and chitosan matrix tablets were studied, 2005.
2. Sahu S *et al.*, formulated and evaluated the sustain release matrix tablet of Atenolol. Atenolol was a beta blocker medication primarily used to treat high blood pressure and heart associated chest pain. Atenolol matrix tablets were prepared by direct compression and wet granulation method using different polymers. All the formulations were evaluated for weight variation, thickness, hardness, friability and dissolution. Tablets of atenolol were prepared utilizing natural polymer chitosan. The formulation F-2 contained chitosan which might have sustained the release since it is also known for its polymeric sustaining effect. The formulation F-2 gave 89.57±0.24% of the drug release in 12 hrs of study, 2008.
3. Ganesh G N K *et al.,* (2010) prepared and evaluated the sustained release matrix tablet of diclofenac sodium using natural polymers such as Cashew nut tree gum, HPMC and Carbopol. It is cleared through the dissolution profile of Diclofenac sodium from matrix tablets prepared using different polymers were indicated an increase in the polymer ratio retarded the drug release to a greater extent.
4. Suriyaprakash T N K *et al.*, developed diclofenac sodium tablets from polymeric matrices [HPMC K-15 and Eudragit NE 30D] and characterization of its physicochemical properties, *In vitro* release studies by using different disintegrants like sodium starch glycollate and polyplasdone in different ratios to optimize its release profile with the standard market product, 2011.
5. Adugna M *et al.*, investigated hydroxypropyl methylcellulose phthalate (HPMCP) and two polymethacrylates, Wangit L30D-55® and Wangit L- 100® for their enteric coating properties using diclofenac sodium tablets as core. The results of the study showed that the polymethacrylates provide better tablet coating properties, 2016.
6. Aparna A *et al.,* formulated and evaluated of Pantoprazole Sodium enteric coated tablets. Pantoprazole sodium is acid labile drug that will degrade in acidic environment of stomach resulting in therapeutic inefficacy. Hence it is necessary to bypass the acidic pH of the stomach which can be achieved by formulating delayed release dosage forms (single unit or multiple units) by using different enteric polymers KOLLICOAT MAE

30DP, AQOAT AS-MF, and Cellulose acetate phthalate as enteric coating polymers, 2016.

7. Jacob S *et al.*, compared the dissolution profile and evaluated the release kinetics of various brands of diclofenac sodium at different gastrointestinal pH levels and verified the *In vitro* dissolution profiles under alcohol-induced dose dumping. Based on the data, it was proved that the pH 4.5 acetate buffer was the most discriminating medium to evaluate the differences between various enteric-coated tablet dosage forms. The similarity factor and release kinetics calculation could help differentiate between the dissolution profiles. Alcohol dumping studies would ensure the dosage form is compliant with the specified standards set by official compendia in spite of significant levels of alcohol, 2016.
8. Jeganathan B *et al.*, prepared and evaluated Diclofenac Sodium Tablet Coated with Polyelectrolyte Multilayer Film Using Hypromellose Acetate Succinate and Polymethacrylates for pH-dependent, modified release drug delivery. In this study, *In vitro* studies were carried out on polyelectrolyte complexes formulated with Eudragit E (EE) and hypromellose acetate succinate (HPMCAS) by non-stoichiometric method. The suitable combination of PEM film based on EE and HPMCAS demonstrated potential candidate for targeted release of DS in the lower part of the gastrointestinal (GI) tract, 2016.