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FORMULATION AND EVALUATION OF BILAYERED TABLETS OF DICLOFENAC SODIUM AND ESOMEPRAZOLE MAGNESIUM- A DUAL THERAPY FOR PEPTIC ULCER

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ABSTRACT

Objective: To formulate a dual therapy of peptic ulcer containing NSAID, Diclofenac sodium and anti-secretary agent Esomeprazole magnesium utilizing the concept of bilayer tablet system which contains Diclofenac sodium as sustained release layer and Esomeprazole magnesium as immediate release layer for the effective treatment gastric/duodenal ulcer. **Method:** The sustained release layer of Diclofenac sodium was prepared by wet granulation technique using polymers like HPMC K15 and Xanthan gum in different concentrations. Sodium bicarbonate was used as a gas generating agent. Immediate release layer of Esomeprazole magnesium was prepared by wet granulation technique using super disintegrants. **Results:** Formulated bilayered tablets were characterized for different parameters like hardness, friability, thickness, weight variation, segregation time, disintegration time, floating lag time and % Cumulative drug release. **Conclusion:** The results of the evaluation tests indicated that the optimized formulation SF1 showed desired release along with and good disintegration time and desired release rate for the Esomeprazole layer. Different formulations were prepared among the formulations the best formulation shows maximum amount of drug release with in12hrs of time period.

KEYWORDS: NSAIDS, Bilayered tablets, Diclofenac sodium, Esomeprazole magnesium.

INTRODUCTION

Oral route of drug administration is the most appealing, convenient, significant and popular route for the delivery of drugs owing to ease of swallowing, self medication and most

economic. Tablets are the most popular and preferred oral formulation available in the market because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids and because it is more tamperproof than capsules.[1-4]

Modified release tablets are coated or uncoated tablet that contain special excipients or they are prepared by special procedures, or both, designed to modify the rate, place or time of release of the active substance(s).[5] Layered tablets, type of modified release, prepared by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each comes from a separate feed frame with individual weight control to form two- or three-layered tablets, depending on the number of separate fills. Each layer may contain a different medicinal agent with varying release profiles.[6]

Among these Bilayer tablet is new era for developing a combination of two or more active pharmaceutical ingredient in single dosage form, Promoting patient convenience and compliance. Dual release tablet is a unit compressed tablet dosage form intended for oral application. It contains 2 layers in which 1 layer having conventional or immediate release part of single or multiple actives; another layer is sustained or controlled release part of single or multiple actives.[7] Combination products-also known as fixed dose combinations are combinations of two or more active drugs produced in a single dosage form. They provide the advantages of combination therapy while reducing the number of prescriptions and the attendant administrative costs and improving patient compliance.

Ideal drugs candidate for bilayer tablet should have the following characteristics

1. Drugs produce additive/synergistic effect (Anti asthmatic; salbutamol+ theophylline)
2. Drugs having opposite side effects may reduce the side effect like (PPIs + NSAIDs and hydrochlorothiazide + amiloride).
3. Incompatible drugs
4. Low biological half-life (ideal for modified release bilayer)
5. Unstable at intestinal pH (ideal for floating bilayer tablets)
6. High first pass metabolism with low biological half-life (ideal for buccoadhesive bilayer).[8]

Diclofenac is an acetic acid nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. Diclofenac sodium (DIC) is its sodium salt belongs to BCS (Biopharmaceutics Classification System) class II drug. IUPAC name is 2-[2-[(2, 6-

dichlorophenyl) amino] phenyl] acetic acid. Diclofenac is 100% absorbed orally and 50% of dose is systematically available. Food has no effect on extent of Diclofenac absorption. The primary mechanism responsible for its anti-inflammatory, antipyretic and analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX) and it appears to inhibit DNA synthesis. Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid. This is also the main side effect of Diclofenac.[9] One major limitation of NSAID use is the risk of serious upper gastrointestinal events, including bleeding, perforation and obstruction, which occur in 1%–2% of users.[10]

Peptic ulcer is an open sore on the lining of the stomach or duodenum. Gastric and duodenal ulcers are produced by an imbalance between mucosal defense mechanism and the damaging force particularly gastric acid and pepsin. Esomeprazole is chemically bis (5-methoxy-2-[(S)-[(4-methoxy-3, 5-dimethyl-2 pyridinyl) methyl] sulfinyl]-1-H-benzimidazole-1-yl), a compound that inhibits gastric acid secretion. Esomeprazole is Anti-Ulcer Agent, Proton-pump Inhibitors and Antihistamines. Its magnesium salt is Esomeprazole magnesium (ESM). It is absorbed completely (90%) after oral administration and the protein binding of Esomeprazole is 97%. Esomeprazole is extensively metabolized in the liver by the Cytochrome P450 (CYP) enzyme system and approximately 80% of an oral dose of Esomeprazole is excreted as inactive metabolites in the urine and the remainder is found as inactive metabolites in the faeces.[11]

NSAIDs are widely prescribed for the treatment of chronic pain along with H2-blocker or PPIs. As the combination in a single dosage form isn't available, the present study has been performed to find out various ways to formulate a tablet dosage form containing a NSAID (Diclofenac sodium) in the sustained release portion and a PPI (Esomeprazole magnesium) in the immediate release portion in order to reduce the incidence of NSAID-induced gastrointestinal injury which may be occurred by not taking anti-ulcerant along with NSAID in case of chronic pain.[12]

The objective of present study is to prepare a bilayer tablets of Diclofenac Sodium (SR) and Esomeprazole magnesium (IR) by using different polymers like, HPMC K15, Xanthane gum, with cross carmellose along with other excipients by combination of both wet granulation and direct compression methods.[13] To evaluate granular blends in terms of Angle of repose, Bulk and tapped density, Carr's index, Hausner's Ratio and to evaluate Bi-

layer matrix tablets in terms of hardness, weight variation, friability, thickness, drug content uniformity, In vitro dissolution studies in 1.2 and 6.8 pH.[14]

MATERIALS AND METHODS

Materials

Esomeprazole magnesium supplied by NATCO Pharma Pvt. Ltd, Kothur, Diclofenac sodium supplied by Qualigens fine chemicals, Mumbai., Lactose - Qualigens fine chemicals, Mumbai. HPMC 15Cps, Sodium Starch Glycolate - NATCO Pharma Pvt. Ltd, Kothur., Starch- Himedia Laboratories Pvt. Ltd, Mumbai., PVPk30 - Himedia Laboratories Pvt. Ltd, Mumbai., Ethyl cellulose, Xanthan gum – Burgoyme Burdiges & Co, Mumbai. All the chemicals and reagents were of high quality analytical grade. Blends of immediate release layer of Esomeprazole magnesium and sustained release layer of Diclofenac sodium were prepared separately. The individual layers were optimized based on the in vitro dissolution data and bilayer tablets were prepared by using the optimized formulae.[13]

Methods

Preformulation

Preformulation studies were conducted for both drugs Esomeprazole magnesium and Diclofenac sodium. For both the drugs preformulation characteristics like Description, Solubility, Melting point, Bulk density, Tapped density, Angle of repose, Hausner's ratio, Compressibility index were performed.

IR absorption spectrum of Esomeprazole magnesium and Diclofenac sodium were recorded using potassium bromide (KBr) pellet method. Assay was performed for both the drugs by following respective methods given in the pharmacopoeias.

Assay of Esomeprazole magnesium.

Transfer about 10 mg of Esomeprazole Magnesium, accurately weighed, to a 200-mL volumetric flask, dissolve in about 10 mL of methanol, add 10 mL of Phosphate buffer pH 11 and dilute with water to volume. This solution contains about 0.05 mg of Esomeprazole magnesium per mL.[8]

Assay of Diclofenac sodium

1. Dissolve about 450 mg Diclofenac Sodium accurately weighed in 25 ml glacial acetic acid and titrated with 0.1 N perchloric acid, determine the end point potentiometrically and Perform blank determination.

2. Each ml 0f 0.1 N Perchloric acid is equivalent to 31.81mg of Diclofenac Sodium.

3. Diclofenac Sodium Assay was found to be 90-110%.[14]

Drug Excipient Compatibility

The compatibility of drugs with their respective excipients was studied by FT-IR spectroscopy. The scanning was performed at scanning speed 2 mm/sec with resolution of 4 cm-1 over the region 4000-400 cm^{-1}. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction.[10]

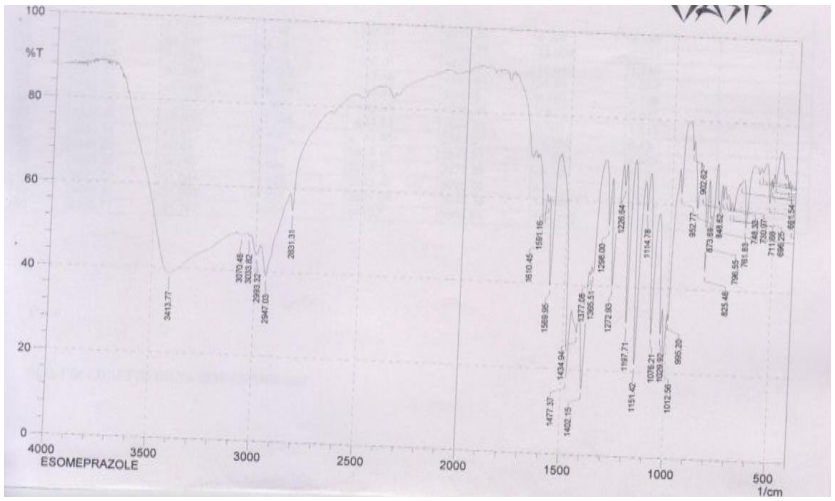

Fig. 1: FTIR of Esomeprazole Magnesium

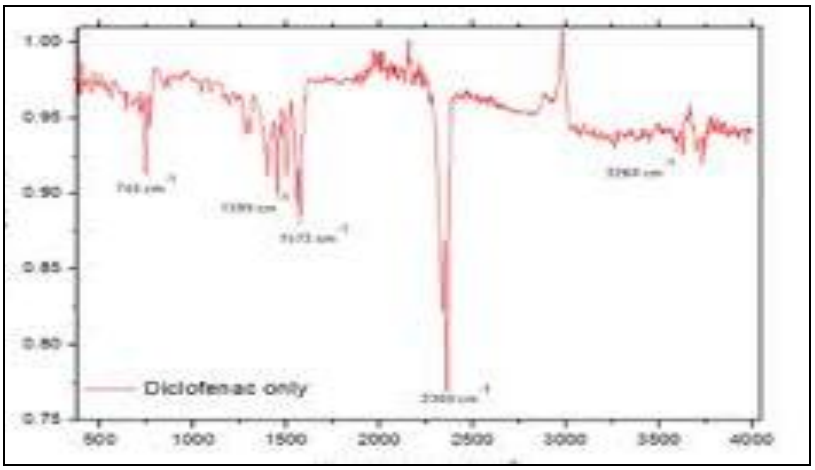

Fig. 2: FTIR of Diclofenac Sodium

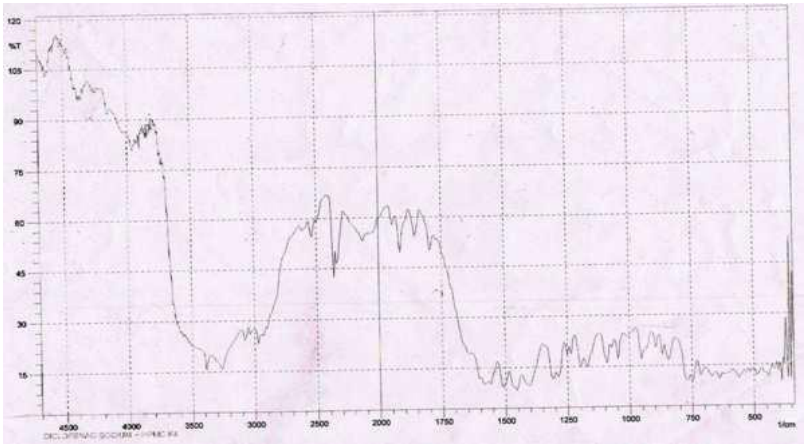

Fig. 3: FTIR of Diclofenac sodium + HPMC + Xanthan gum

Table 1: Calibration curve for Esomeprazole magnesium

S.No	Concentration (mcg/ml)	UV Absorbance At 301 nm
1.	0	0
2.	2	0.068
3.	4	0.142
4.	6	0.236
5.	8	0.302
6.	10	0.347

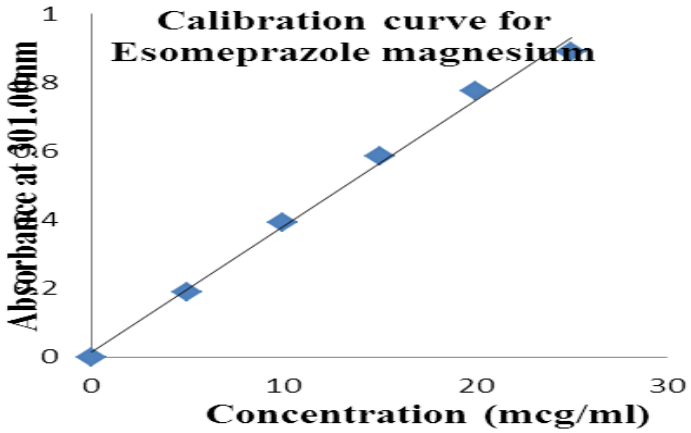

Fig.4: Calibration curve of Esomeprazole magnesium

Table 2: Calibration curve for Diclofenac sodium

S.No	Concentration (mcg/ml)	UV Absorbance At 280 nm
1.	0	0
2.	5.0	0.189
3.	10	0.390
4.	15	0.586
5.	20	0.776
6.	25	0.890

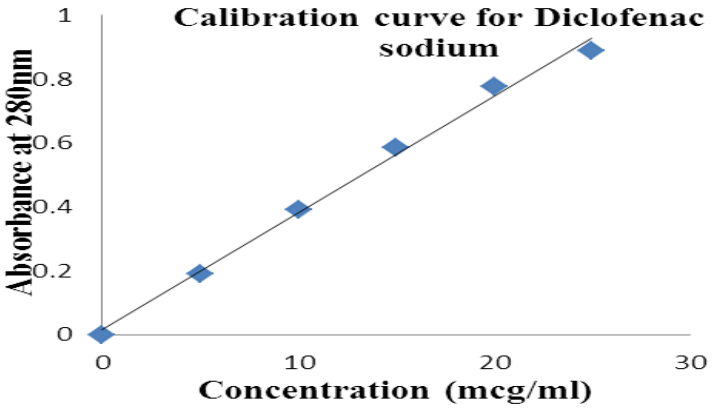

Fig.5: Calibration curve of Diclofenac sodium

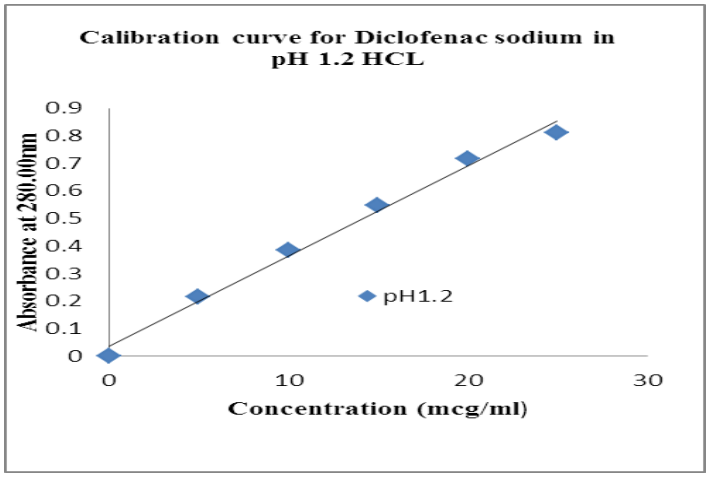

Fig.6: Calibration curve of Diclofenac sodium at pH 1.2 HCL

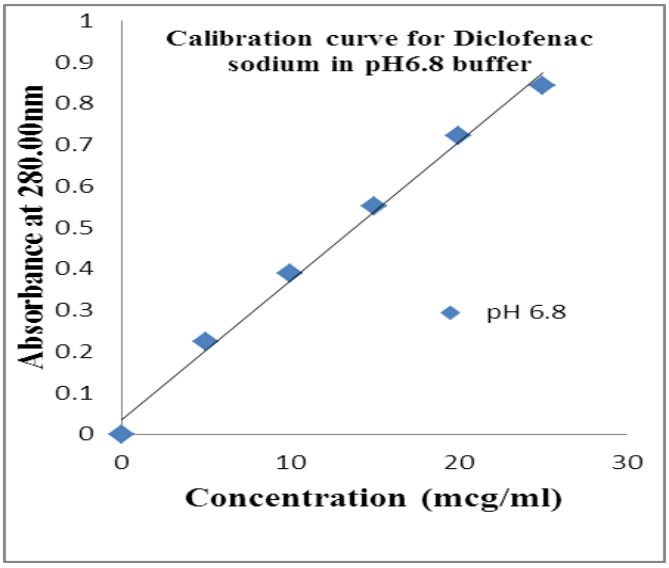

Fig.7: Calibration curve of Diclofenac sodium at pH 6.8 buffer

Preparation of Diclofenac Sodium Blend

Esomeprazole magnesium immediate release layer tablets were prepared by wet granulation method and other excipients like Sodium Bicarbonate and pregelatinised Starch were sifted through sieve no 40 #. The sifted powders were thoroughly mixed for approximately 5 min and again passed through sieve no 40 # for maintaining uniformity in particle size. Iso Propyl Alcohol having 5% w/v amount of PVP K30 was used as the granulating liquid and the solution was added to the mixture in step 2 and was kneaded for 2-5 min, then the kneaded mass was passed through sieve no # 20 to obtain the granules. The granules obtained in step 3 were dried in a tray drier at 50°C for 2 hrs. The dried granules were lubricated uniformly with weighed quantities of magnesium stearate and aerosil. The above granules were compressed into tablets by tablet compression machine. Compressed final blend using Double rotary, D-tooling, bilayer compression machine using 12 mm round shaped punches and corresponding dies. Formulation code for the different batches is marked as F1, F2, F3, F4, F5, F6, F7, F8 & F9 and for bilayer Tablets as BF1, BF2, BF3, BF4, BF5,BF6 and BF7.[15]

Preparation of Diclofenac Sodium Blend by Wet Granulation Method

The composition of different formulas of Diclofenac Sodium tablets is shown in table (4), Formula (DF1to DF6) prepared by utilizing wet granulation process. In wet granulation technique; required quantities of drug, polymer(s) and diluent enough to prepare 50 tablets were weighed and mixed uniformly using mortar and pestle, after sufficient time of dry blending of ingredients in mortar, granulating solutions was added at slow rate in the form of fine droplets. Then kneaded until satisfactory consistency was achieved (ball test).[7] The wet mass was granulated by passing through sieve no. 10, the granulated mass was air dried at room temperature for 30 min. and then dried in tray drier at 40 ˚C for 30 min., knowing weight of granules were mixed with calculated amount of magnesium stearate and talc powder for 3 min. then compressed using 12 mm flat face punch tableting machine. Formulation code for the different batches is marked as DF1, DF2, DF3, DF4, DF5 and DF6, and for bilayer Tablets as BF1, BF2, BF3, BF4, BF5, BF6 and BF7.[16]

Table 3: Composition of Esomeprazole magnesium blend.

S. No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Esomeprazole magnesium	20	20	20	20	20	20	20	20	20
2	Crosscarmelose sodium	6	8	10	-	-	-	-	-	-

3	Crosspovidone	-	-	-	6	8	10	-	-	-
4	Sodium starch Glycolate	-	-	-	-	-	-	6	8	10
5	Lactose	70	65	60	70	65	60	70	65	60
6	Sodium bicarbonate	150	150	150	150	150	150	150	150	150
7	Magnesium Stearate	2%	2%	2%	2%	2%	2%	2%	2%	2%
8	Aerosil	1%	1%	1%	1%	1%	1%	1%	1%	1%
9	PVP-K30	5% PVP IN IPA (q.s)								
10	Total weight	250	250	250	250	250	250	250	250	250

Table 4: Composition of Diclofenac Sodium blend.

S.No	Ingredients	Composition(Mg) for 10 Tablets						
		DF1	DF2	DF3	DF4	DF5	DF6	DF7
1	Diclofenac sodium	1000	1000	1000	1000	1000	1000	1000
2	HPMC 15 cps	500	750	1000	-	-	-	500
3	Xanthane gum	-	-	-	500	750	1000	500
4	Lactose	800	550	300	800	550	300	300
5	PVP-K30	10	10	10	10	10	10	10
6	Aerosil	2	2	2	2	2	2	2
7	Talc	4	4	4	4	4	4	4
8	Magnesium sterate	4	4	4	4	4	4	4
9	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 5: Composition of Optimised Bilayered Tablet.

S.No	Ingredients	Qty.(mg)	Ingredients	Qty.(mg)
1	Diclofenac sodium	100	Esomeprazole magnesium	20
2	HPMC 15 cps	50	Sodium starch glycolate	10
3	Xanthane gum	50	Sodium bicarbonate	150
4	Lactose	30	Lactose	60
5	PVP-K30	`10	Magnesium stearate	2%
6	Aerosil	2%	Talc	1%
7	Talc	1%	PVP K 30	5% PVP in IPA
8	Magnesium state	**1%**	-	-
9	Purified Water	**q.s**	-	-
10	**Total weight**	**250**	**Total weight**	**250**

Evaluation

The prepared formulations were evaluated for the following parameters:

Pre-compression evaluation

Angle of Repose

The angle of repose of granules or powder was determined by the funnel method. The accurately weight granules or powder were taken in the funnel. The granules or powder were

allowed to flow through the funnel freely on to the surface. The diameter of the granules or powder cone was measured and angle of repose was calculated using the following equation[13]:

$\tan \theta = h/ r$ or $\theta = \tan^{-1} (h/ r)$

Where, θ = angle of repose,

h = height of the cone, and

r = radius of the cone base

Bulk Density

Bulk density (Db) was determined by measuring the volume (Vb) of known weighed quantity (W) of granules or powder using bulk density apparatus and can be calculated by using the formula[15]:

$Db = W/ Vb$

Tapped Density

Tapped density (Dt) was determined by measuring the volume (Vt) of known weighed quantity (W) of granules or powder using bulk density apparatus and can be calculated by using the formula[15]:

$Dt = W/ Vt$

Carr's Index

The Carr's index (% compressibility) of the granules or powder was calculated from the difference between the tapped and bulk densities divided by the tapped density and the ratio expressed as a percentage.[16]

$$\text{Carr's Index (\%)} = \frac{Dt - Db}{Dt} \text{ X } 100$$

Where, Dt is the tapped density and Db is the bulk density.

Hausner's ratio

The Hausner's ratio was calculated by dividing the tapped density by the bulk density of the granules.[15]

Hausner's ratio = Dt/Db

Where, Dt is the tapped density and Db is the bulk density.

Table 6 Evaluation Of Flow And Derived Properties Of API & Granules

Formulation	Angle Of Repose (n=3) ± S.D	Bulk Density (g/ml) (n=3) ± S.D	Tapped density (g/ml) (n=3) ± S.D	Carr's index (%) (n=3) ± S.D	Hausner's Ratio (n=3) ± S.D
Pure drug(ESM)	26.14±0.12	0.355±0.06	0.426±0.04	16.89±0.66	1.20±0.05
Pure drug(DF)	19.66±0.15	0.505±0.06	0.589±0.02	14.22±0.04	1.16±0.07
ESM,					
F1	27.44±0.15	0.387±0.08	0.472±0.02	17.89±0.34	1.21±0.01
F2	26.28±0.02	0.358±0.06	0.461±0.04	15.98±0.26	1.16±0.06
F3	26.56±0.08	0.356±0.02	0.452±0.03	16.68±0.36	1.12±0.02
F4	25.24±0.02	0.352±0.03	0.446±0.02	15.48±0.63	1.18±0.04
F5	26.68±0.16	0.358±0.05	0.450±0.06	17.26±0.24	1.15±0.01
F6	25.96±0.12	0.357±0.06	0.453±0.05	15.24±0.42	1.20±0.07
F7	27.24±0.32	0.360±0.02	0.448±0.03	17.22±0.22	1.22±0.06
F8	25.36±0.48	0.356±0.05	0.447±0.02	16.88±0.28	1.19±0.05
F9	25.26±0.42	0.352±0.02	0.442±0.04	15.66±0.32	1.20±0.01
DF1	20.06±0.12	0.553±0.06	0.646±0.04	14.46±0.68	1.168±0.05
DF2	21.26±0.13	0.536±0.08	0.626±0.07	14.33±0.25	1.167±0.07
DF3	20.24±0.15	0.539±0.12	0.629±0.09	14.42±0.35	1.166±0.05
DF4	22.14±0.08	0.546±0.08	0.641±0.08	14.78±0.26	1.173±0.09
DF5	22.72±0.26	0.542±0.09	0.636±0.07	14.69±0.68	1.173±0.07
DF6	20.16±0.18	0.511±0.09	0.600±0.06	14.88±0.41	1.174±0.06
DF7	21.33±0.08	0.552±0.07	0.648±0.06	14.75±0.55	1.173±0.07
n=3 ± S.D= Standard Deviation					

Post compression studies

Shape of Tablet

Compressed tablets were examined under the magnifying lens.

Tablet Dimensions

Thickness was measured by using Vernier calipers.

Weight variation Test

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.[16]

Hardness

The hardness of 5 tablets from each of the prepared formulas was measured individually using Monsanto hardness tester.[16]

Friability test

The friability test was done for the prepared tablet using Roche friabilator, the friability was calculated as the percent weight loss, after 100 revolutions of 20 tablets from each formula.[17] It is expressed in percentage (%). Twenty tablets were initially weighed (W1) and transferred into friabilator. The friabilator was operated at 25 RPM for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W2). The % friability calculated by

% Friability = (W1-W2) / W1 X 100

Where, W1 = Weight of tablets before test

W2 = Weight of tablets after test

Content uniformity test

5 tablets from each prepared formulas were crushed in a mortar then weight of one tablet were dissolved using 0.1N HCL for Diclofenac sodium and phosphate buffer pH 6.8 for Esomeprazole magnesium as the solvent respectively. The amount of Diclofenac sodium and Esomeprazole magnesium was determined by employing UV absorption at the wave length of maximum absorbance which is about 280nm for Diclofenac sodium and 301nm for Esomeprazole magnesium.[18]

Dissolution test

The in vitro release study of each formula was conducted in USP dissolution apparatus (basket) in 900 ml 0.1 N HCL (pH1.2) for first 2 hrs, then in 900 ml phosphate buffer (pH 6.8) for the rest of experiment, at 37 ± 2ºC and at 50 rpm under sink condition. Samples of 5 ml were withdrawn at specific time intervals, then filtered, diluted and analyzed spectrophotometrically at the wave length of maximum absorbance for each drug.[19]

Determination of the Release Kinetics

To study the mechanism of drug release from the selected formula, the release data were fitted to various release kinetic models include zero order, first order and Higuchi equations. Furthermore, to characterize the release behavior i.e. to understand the mechanism, Korsmeyer – Peppa's model was applied.[13]

$$Mt / M\infty = KKP\ t^{n}$$

Where Mt and M∞ are cumulative amounts of drug release at time t and infinite time (i.e. fraction of drug release at time t), KKP is the constant incorporating structural and

geometrical characteristics of controlled release device; and n is the diffusion exponent indicative of the mechanism of drug release.[14]

Table 7: Post Compression Parameters of the Bilayered Tablets BF1-BF7

Formulation Code	Weight Variation	Hardness (n=3) ± S.D	Thickness (mm) (n=3) ± S.D	Friability (n=3) ± S.D
BF1	Pass	5.9 ± 0.36	3.1 ± 0.06	0.36 ± 0.11
BF2	Pass	5.5 ± 0.59	2.9 ± 0.02	0.42 ± 0.12
BF3	Pass	5.7 ± 0.26	3.0 ± 0.03	0.39 ± 0.06
BF4	Pass	6.1 ± 0.58	2.9 ± 0.04	0.41 ± 0.14
BF5	Pass	5.8 ± 0.22	3.1 ± 0.06	0.45 ± 0.11
BF6	Pass	5.6 ± 0.34	3.0 ± 0.02	0.42 ± 0.12
BF7	Pass	5.8 ± 0.38	2.9 ± 0.02	0.26 ± 0.13
n=3 ± S.D= Standard Deviation				

Table 8: Post Compression Parameters Of The Bilayered Tablets BF1-BF7

Formulation Code	Swelling index (%) (n=3)	Disintegration Time (sec) (n=3)	Drug content	
			ESM	DIC
BF1	42.34 ± 0.26	95 ± 2	98.86	100.2
BF2	47.33 ± 0.32	96 ± 3	99.22	98.86
BF3	47.75 ± 0.28	98 ± 2	97.54	100.8
BF4	32.23 ± 0.22	95 ± 4	96.42	99.26
BF5	48.66 ± 0.16	98 ± 2	98.28	98.28
BF6	47.72 ± 0.28	95 ± 4	99.26	97.78
BF7	**46.63** ± 0.26	98 ± 2	98.64	99.52
n=3 ± S.D= Standard Deviation				

Table 9: % Cumulative Drug Release Of Esomeprazole Tablets

Time	% Cumulative Drug Release (% CDR)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	70	72	82	72	75	82	75	78	85
15	72	75	85	75	78	85	79	82	90
30	79	81	89	79	82	88	82	86	95
45	83	86	93	84	88	92	85	90	98
60	86	90	97	88	92	98	92	98	
70	90	94		91	95				

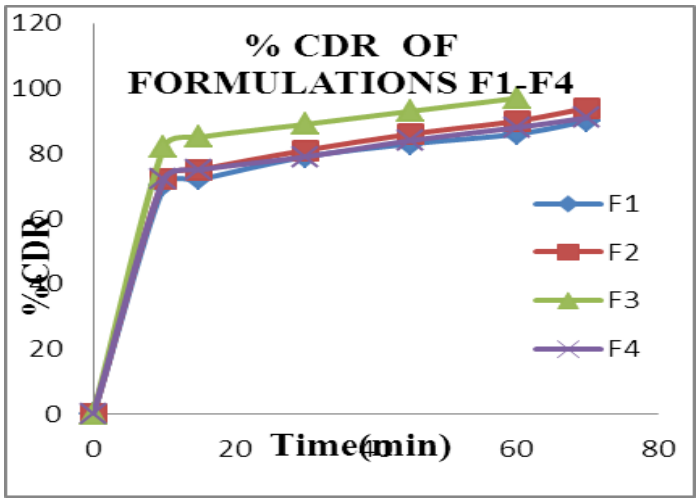

Fig.8: % Cumulative Drug Release plots for formulations F1-F4.

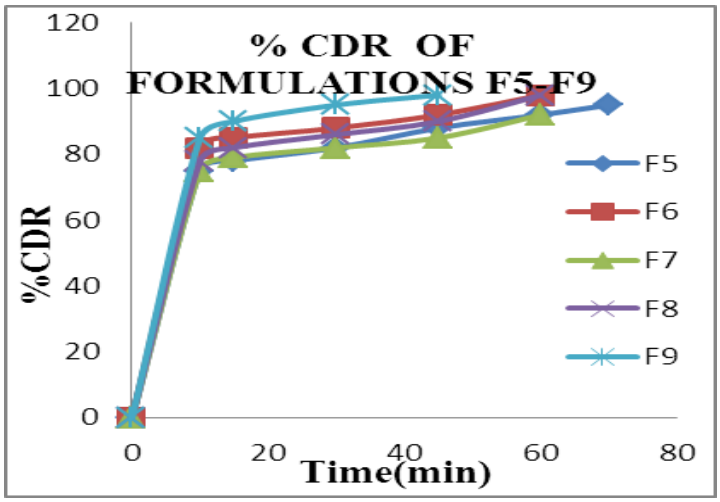

Fig.9: % Cumulative Drug Release plots for formulations F5-F9.

Table 10: Dissolution Studies Of Formulations BF1-BF7:

S.No	Drug	Time	Percent Drug Release						
			BF1	BF2	BF3	BF4	BF5	BF6	BF7
1	ESM (F9)	0 min	0	0	0	0	0	0	0
		10 min	85	82	86	82	86	83	84
		15 min	90	89	91	90	91	89	92
		30 min	95	95	96	94	95	91	94
		45 min	98	98	99	98	98	97	99
2	DIC	1st hr	8.21	10.16	14.46	7.68	8.92	10.22	8.86
		2nd hr	21.66	24.48	28.12	18.46	14.46	14.48	14.64
		3rd hr	45.75	39.43	38.46	35.45	28.66	26.63	29.22
		4th hr	75.22	59.28	46.17	58.96	44.68	42.26	36.44
		6th hr	97.15	70.64	59.35	70.16	58.45	55.67	48.28
		7th hr		81.25	64.54	82.46	69.23	68.28	56.74
		8th hr		98.86	76.43	94.48	78.45	74.42	67.63
		9th hr			82.56		86.92	82.68	76.28
		10th hr			99.27		97.56	90.16	84.53

		11th hr						98.28	91.26
		12th hr							99.57
		12th hr							99.57

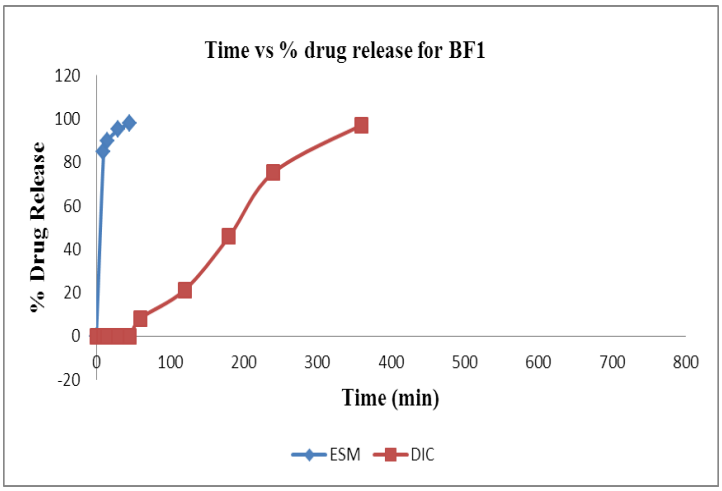

Fig.10: Time Vs % Drug Release Plot For BF-1

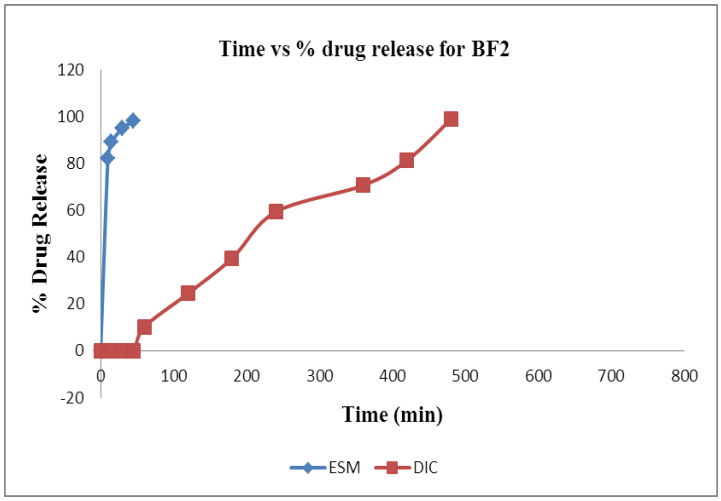

Fig.11: Time Vs % Drug Release plot for BF-2

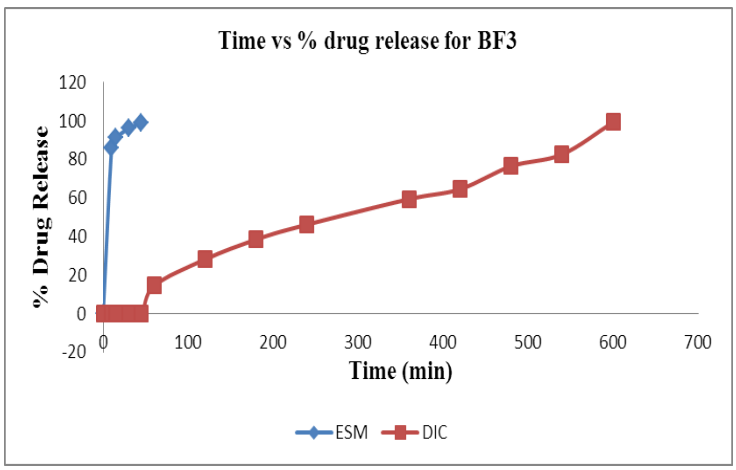

Fig.12: Time Vs % Drug Release plot for BF-3

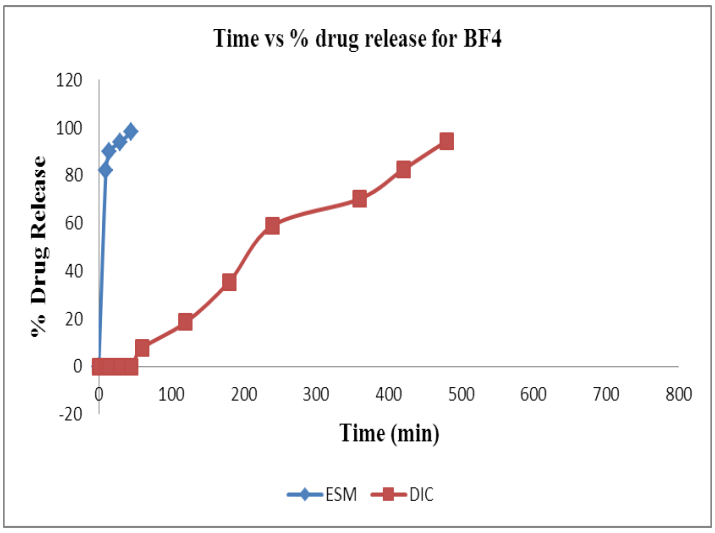

Fig.13: Time Vs % Drug Release plot for BF-4

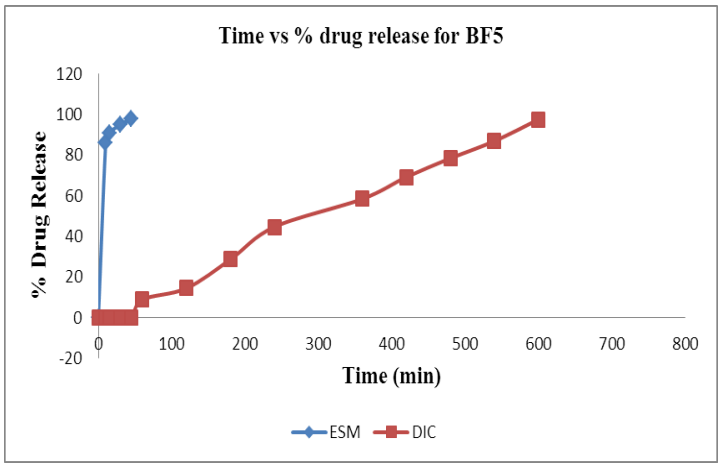

Fig.14: Time Vs % Drug Release plot for BF-5

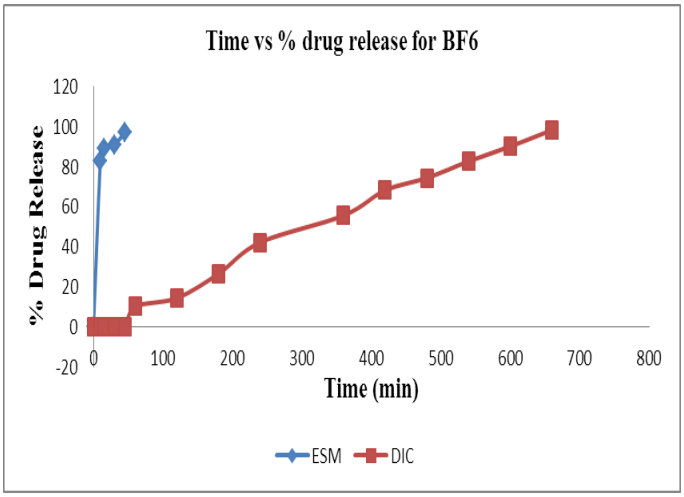

Fig.15: Time Vs % Drug Release plot for BF-6

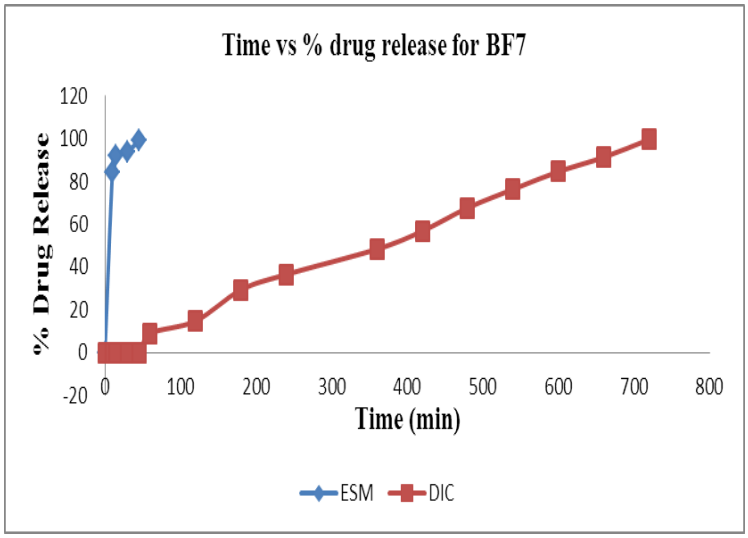

Fig.16: Time Vs % Drug Release plot for BF-7

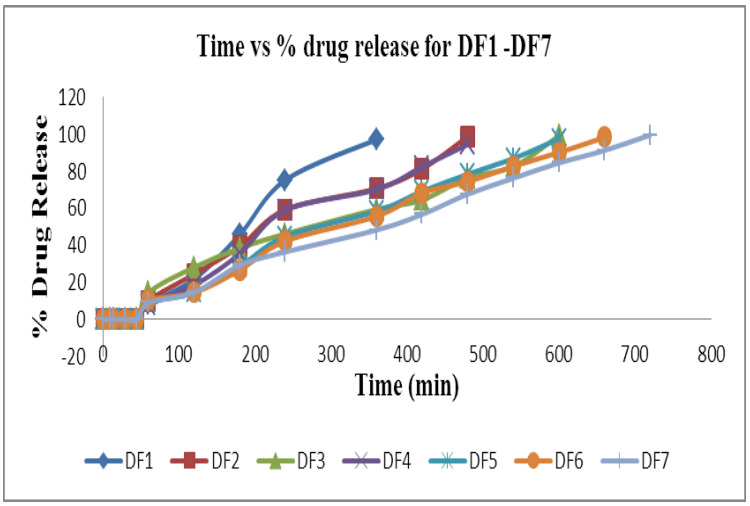

Fig.17: Time Vs % Drug Release plot for BF-1 TO BF7

RESULTS AND DISCUSSION

Preformulation studies of pure drug

Esomeprazole magnesium was found to be yellowish in colour and odourless; DIC is a clear, transparent and colourless to slightly yellowish in colour. The IR spectra of pure drugs (Figure No.1, 2) were found to be similar to the reference standard IR spectrum of ESM & DIC given in British pharmacopoeia. The IR spectrum of DIC in combination with other exciepients (Figure No.3) shows that there is no interaction between drug and exciepients.

Melting point of ESM was found to be in the range of 178°C to 183°C & Melting point of DIC was found to be in the range of 156°C to 158°C with decomposition as reported in pharmacopoeia, thus indicating purity of the drug sample.

Solubility Studies

The solubility study of ESM in different solvent suggests that the drug is maximum soluble in methanol and minimum soluble in light liquid paraffin than other solvent. Descending order of solubility in different solvents-

Methanol > Ethanol > pH 7.4 buffer > Chloroform > Acetone > Tween 80 > Span 80 > n-hexane > light liquid paraffin.

DIC is freely soluble in methanol, soluble in ethanol, sparingly soluble in water, slightly soluble in acetone and partially insoluble in ether.

The partition coefficient of ESM between octanol and water was found to be 4.52 and log P value was 0.655368, which showed that ESM is lipophillic in nature. In n-octanol/water partition coefficient of DIC is 13.4.

Pre compressional parameters

Characterization of granules

The granules prepared in the formulation were subjected for characterization of flow and derived properties. From the results it was shown that the bulk density of granules of ESM and pure drugs are 0.355 gm/ml,0.387 gm/ml respectively and that of DIC pure drug is 0.505 gm/ml, DIC granules are within the range of 0.511-0.554 gm/ml, tapped density values for pure ESM and its granules are 0.426 g/ml and 0.472 g/ml respectively and that of Pure DIC is 0.589 gm/ml, DIC granules are within the range of 0.6-0.646 gm/ml. These values were also given (in the Table 6), indicating excellent flow properties for both the pure drug and granules.

Post compressional evaluation

The thickness of the bilayered tablets was found to be within the range of 2.9 to 3.1mm. The hardness of the bilayered tablets was found to be within the range of 5.5 to 6.1 kg/cm. The friability of bilayered tablets was found to be within the range of 0.26 to 0.45%. The drug content in granules was in the range of 98-99%. The tablets were considered completely disintegrated and their disintegration range was found to be in range of 95 to 98sec. The swelling index of all the tablet formulations was found to be within the range of 32.23 to 48.66%.

Dissolution studies

In-vitro release profiles of bilayered tablets during 12hrs studies were found to have very good sustaining efficacy. Among all Esomeprazole formulations F9 shows maximum amount of drug release within short period of time. Hence it is selected for designing bilayered tablet formulation. In the formulated bilayered tablets immediate release layer containing Esomeprazole magnesium releases 98-99% of drug in all the formulations within 45mins. But in the sustained release portion, Formulation DF-1 Containing HPMC polymer in least quantity releases the maximum amount of drug in 6^{th} hr. The formulation DF-2 containing same HPMC polymer in little higher quantity release the maximum amount of drug in 8^{th}hr, The formulation DF-3 containing same HPMC polymer in higher quantity release the maximum amount of drug in 10^{th}hr. Same quantities of another polymer i.e., xanthan gum are DF-4, DF-5 and DF-6 release maximum amount of drug in 8^{th}hr,10^{th} hr and 11^{th} hrs respectively but the amount of drug release is very low than the above three formulations. so combinations of these two polymers in equal quantity are assessed by the subsequent formulation DF-7 shows 99.57% release in 12hrs, order of drug release among all the formulations was DF-7 > DF-2 > DF-6 > DF-5 >DF-1 > DF-4.

CONCLUSION

In the present study bilayer tablets of Esomeprazole magnesium and Diclofenac sodium as immediate and sustained release combination would be used to improve patient compliance towards the effective management of pain, rheumatoid arthritis, osteo- arthritis and post operative pain without the side effect of gastric irritation. Esomeprazole magnesium was formulated as immediate release layer using super disintegrant and Diclofenac sodium was prepared as sustained release layer using matrix forming polymers like HPMC and Xanthan gum. Hydrophilic matrix of HPMC alone could not control the Diclofenac sodium release effectively for 12 h whereas when combined with xanthan gum could slow down the release of drug from their matrices and can be successfully employed for formulating sustained-release matrix tablets. Diffusion coupled with erosion might be the mechanism for the drug release which can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional tablets.

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