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Formulation and Evaluation of Bilayer Tablet of Diclofenac Sodium and Misoprostol

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ABSTRACT:
The objective of this research was to formulate bi-layer tablet which contains immediate-release layer of Misoprostol for quick onset of action and sustained release of Diclofenac sodium for prolonging long period. In the Study of Formulation of Bilayer tablet following materials using as immediate release and Starch IP, Croscarmellose Sodium IP, Microcrystalline vivapur 12, Microcrystalline PH 101, Crospovidone, Magnesium Stearate IP, Colloidal silicon dioxide IP, Talc IP, in different ratios as release retardant materials using a wet granulation method. The sustained release layer of Diclofenac sodium was prepared using Hydroxy propyl methyl cellouse IP, Microcrystalline cellulose IP, Sodium carboxy methyl cellulose IP, Xantham gum, Povidone IP K-30 and K-90, Colloidal silicon dioxide IP along with other excipients such as Magnesium Stearate IP, Talc IP by wet granulation technique. The release rate of Misoprostol from Formulations 6 was 99.31% at 75 min. The release rate of Diclofenac sodium from Formulations 6 was 98.92% at 24hr. All tablets exhibited good physical properties with Respect to appearance, content uniformity, hardness, weight variation and Invitro dissolution. The bilayer tablets were prepared and show good release rate.

KEY WORD: Wet Granulation Method, Immediate release, Sustained release, Diclofenac sodium, Misoprostol.

I. INTRODUCTION:

Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer tablets are novel drug delivery systems where a combination of two or more drugs in a single unit. Bi-layer tablet is suitable for sequential release of two drugs in combination in which one layer is for immediate release and second layer is sustained release. Hence, the use of bi-layer tablets is a very different aspect for anti-inflammatory, analgesic, diabetic, and anti-hypertensive drugs where combination therapy is often used.

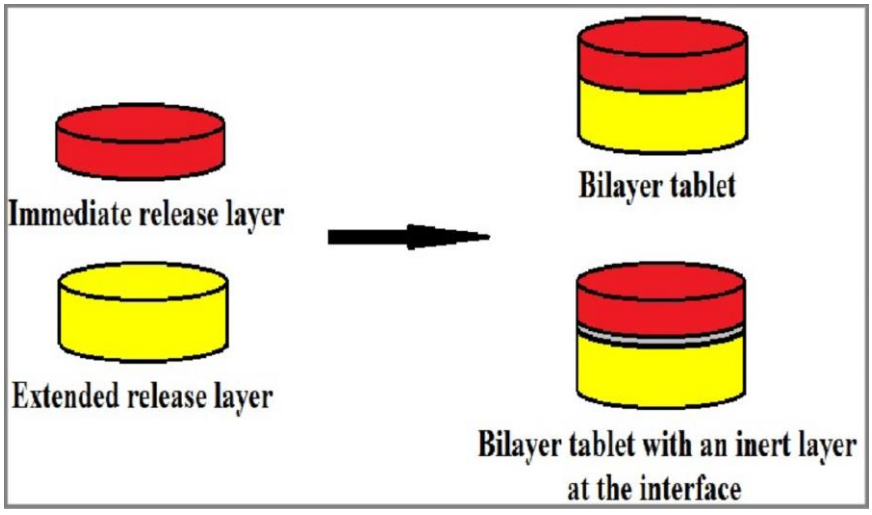

Figure No: 1 Bilayer tablet

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II. DRUG PROFILE:

2.1 Diclofenac Sodium:

Diclofenac sodium is the sodium salt of diclofenac. It contains a diclofenac(1-). Diclofenac Sodium is the sodium salt form of diclofenac, a benzene acetic acid derivate and nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory activity.

- **Formula :** $C_{14}H_{11}Cl_2NO_2$
- **Molar mass :** 296.149 g·mol−1
- **Density :** 1.4±0.1 g/cm3
- **Melting point :** 279-289°C
- **Boiling point :** 412.0±45.0 °C at 760 mmHg
- **Protein binding:** over 99.7% bound to serum proteins, primarily albumin.
- **Trade names:** Cataflam, Voltaren-XR, Dyloject, Cambia, Zipsor, and Zorvolex.
- **Elimination half-life:** 1.5 hr.
- **Bioavailability:** almost completely absorbed after oral administration
- **Excretion:** Kidney (urine)

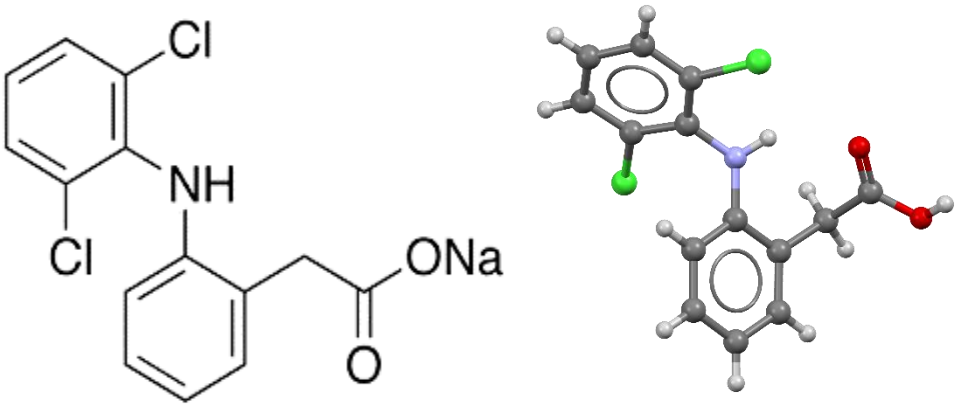

Figure No: 2 Structure Of Diclofenac sodium

2.2 Misoprostol:

Misoprostol is a synthetic prostaglandin medication used to prevent and treat stomach and duodenal ulcers, induce labor, cause an abortion, and treat postpartum bleeding due to poor contraction of the uterus. Misoprostol is taken by mouth when used to prevent gastric ulcers in persons taking NSAIDs.

- **Formula :** $C_{22}H_{38}O_5$
- **Molar mass :** 382.5 g·mol−1
- **Density :** 1.189 g/cm3
- **Color :** white in color
- **Solubility :** soluble in ethanol
- **Melting point :** 263°C
- **Boiling point :** 497 °C at 760 mmHg
- **Protein binding:** 80–90% (active metabolite, misoprostol acid).
- **Trade names:** Cytotec.
- **ATC code:** A02BB01 (WHO) G02AD06 (WHO)
- **Routes of administration:** By mouth, rectal vaginal, under the tongue.
- **Elimination half-life:** 20-40min.
- **Metabolism:** Liver (extensive to misoprostic acid)
- **Bioavailability:** extensively absorbed.
- **Excretion:** Kidney (urine)

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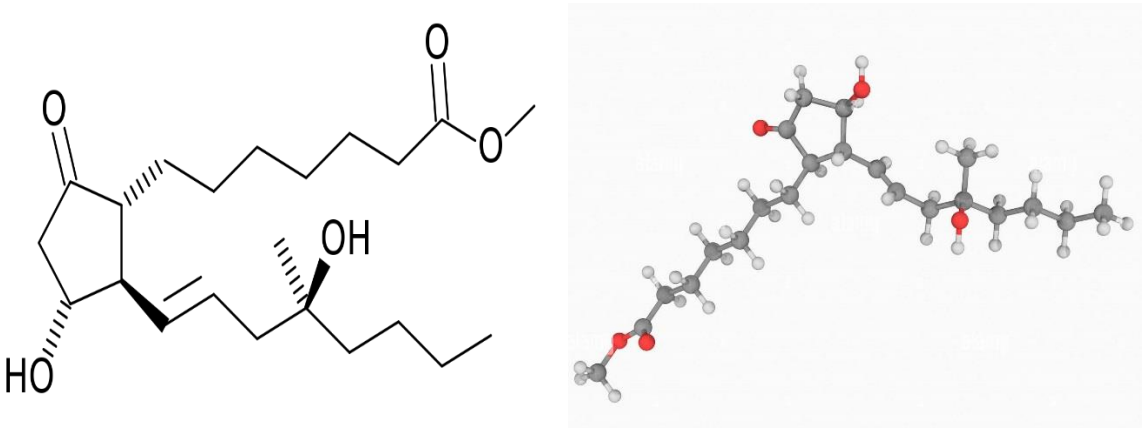

Figure No: 3 Structure Of Misoprostol

III. MATERIALS AND METHODS:

3.1 DRUGS AND EXCIPIENTS:

List of chemicals used in Diclofenac sodium, Misoprostol, Starch IP, Croscarmellose Sodium IP, Microcrystalline vivapur 12, Microcrystalline PH 101, Crospovidone, Magnesium Stearate IP, Colloidal silicon dioxide IP, Talc IP, Hydroxy propyl methyl cellouse IP, Microcrystalline cellulose IP, Sodium carboxy methyl cellulose IP, Xantham gum, Povidone IP K-30 and K-90, sunset yellow lake, Isopropyl alcohol, water.

3.2 METHODOLOGY:

3.2.1. Procedure for IR:

Sieving:

Sift total dispensed quantity of Misoprostol in HPMC along with croscarmellose sodium through 40-mesh (420µm) and collected. Sift total dispensed quantity of Crospovidone through 40 mesh and collected. Sift total dispensed quantity of MCC (Vivapur 12) along with Sunset yellow lake through 40- mesh (420µm) and collected. Total dispensed quantity of Magnesium stearate (Lubrication) sifted through 40-mesh (420µm) and collected into a poly bags appropriately labeled.

Blending & Lubrication:

Transfer the sifted materials into nearby blender-200 lits. Added the total quantity of sifted materials Misoprostol 1% HPMC along with croscarmellose sodium, MCC along with sunset yellow lake, Crospovidone into the blender for 15 minutes at 10 RPM. The above pre-Blend again sifted through 40 # sieve and collected into bag. Load total quantity of above sifted pre blend into bin and seal blender bin and mix for 10 minutes at 10 RPM. Add total quantity of sifted (40 # mesh) Magnesium Stearate to the above blender bin and mix for 5 minutes at 10 RPM. Store the lubricated granules in IPC lined with double poly bag with product identity, manufacture date, batch number and quantity. Until required for tableting, the lubricated granules is stored in a secure holding area NMT 26℃ and RH should be not more than 60%. Maximum hold time of lubricated granules is NMT 7 days from date of lubrication.

3.2.2. Procedure for SR:

Sieving: (Dry Mix part)

Sift separately lot wise quantity of Diclofenac sodium, HPMC K100M, MCC, sodium Carboxy methyl cellulose through 40# sieve and transfer to RMG by using Pneumatic transfer system.

Sieving: (Lubrication part)

Sift total dispensed quantity of HPMC K4M (Extra granular), Magnesium stearate through 40 mesh (420µm) sieve and collect into a clean double bag. Sift total dispensed quantity (Extra granular) of talc along with colloidal silicon dioxide through 40-mesh (420µm) sieve and collected.

Binder Solution Preparation:

In a suitable stainless steel vessel fitted with stirrer, add Isopropyl alcohol and purified water and mix well and start continuous stirring with required RPM to form a vortex. Add separately lot I & II quantity of Povidone slowly into the vortex to form a viscous solution.

Blending & Lubrication:

Transfer the IPC bin containing Diclofenac sodium layer granules into blending area. Transfer the granules (dried & sized granules) into the Double cone blender and seal the blender bin and blend for 5 minutes at 10 RPM Transfer the total quantity of

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(sifted through 40 # mesh) HPMC K4M, talc with colloidal silicon dioxide into Blender Bin by using pneumatic transfer system and seal the blender bin and mix for 15 minutes at 10 RPM. Transfer the total quantity of sifted (40 # mesh sieve) Magnesium Stearate to the above blender bin by using pneumatic transfer system and seal the blender bin and mix for 5 minutes at 10 RPM. Unload and Store the lubricated granules in IPC bin and labeled with the product identity, manufacture date, batch number and quantity. Until required for tablet, the bulk lubricated granules is stored in a secure holding area NMT 26℃ and RH should be not more than 60%.

3.2.3. Compression:

Set the compression machine with 9.55 mm round shaped shallow concave punches and dies. Allow the lubricated granules to flow into the machine and start the machine. If required pre compression force also apply for the tablet compression. Continue compression after setting all the quality parameters. Pass the compressed tablets through de-duster and metal detector. Limit of Machine speed: 10 RPM to 30 RPM. Collect the tablets in clean IPC/Bulk containers lined with double black poly bag. Check the proper functioning of the metal detector at the start and end of compression.

RAW MATERIALS	F1	F2	F3	F4	F5	F6
MISOPROSTOL	10	10	10	10	10	10
STARCH IP	37	37	35	-	-	-
CROSCARMELLOSE SODIUM IP	5	-	7	5	5.5	5.5
MICROCRYSTALLINE VIVAPUR 12	25	-	-	-	54.5	52.5
MICROCRYSTALLINE PH 101	-	30	25	56.5	-	-
CROSPOVIDONE IP	-	-	-	5	7.5	10
SUNSET YELLOW LAKE HIS	1	1	0.5	0.5	0.5	0.5
MAGNESIUM STEARATE IP	1	1	1.5	1.5	1	1.5
COLLOIDAL SILICON DIOXIDE IP	-	1	-	-	1	-
TALC IP	1	-	1	1.5	-	-
DICLOFENAC	200	200	200	200	200	200
HYDROXY PROPYL METHYL CELLOUSE IP	25	25	35	35	40	40
MICROCRYSTALLINE CELLULOSE IP	25	25	5	-	8	5
SODIUM CARBOXY METHYL CELLULOSE IP	10	-	5	2	-	-
XANTHAM GUM	-	10	15	20	6	8
POVIDONE IP K-30	5	5	5	5	-	-
POVIDONE IP K-90	-	-	-	-	5	5
COLLOIDAL SILICON DIOXIDE IP	1	2	-	2	1	2
MAGNESIUM STEARATE	2	1.5	2.5	3	5	5
TALC IP	2	1.5	2.5	3	5	5
TOTEL	350mg	350mg	350mg	350mg	350mg	350mg

Table No: 1 Formulation Table

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Figure No: 4 IR & SR Granules

Figure No: 5 Bilayer Tablet Of Diclofenac & Misoprostol

IV. EVALUATION PARAMETERS:

4.1 RAW MATERIAL ANALYSIS:

4.1.1 Description:

Appearance of the materials was noted, compared with specified monograph or with standard materials.

4.1.2 Identification:

Identification is the important parameter for Qualitative Analysis of materials. Material was identified by chemical and FT-IR method.

4.1.3 Solubility Analysis:

Solubility is an important parameter for preformulation studies because: It affects the dissolution of drug. Bioavailability of drug is directly affected by dissolution and absorption of drug by oral administration. Particle size, shape, surface area may affects the dissolution characteristics of drug hence it should be determined during preformulation.

4.1.4 Loss on drying (%):

1g of drug was accurately weighed and dried in an oven at 105°C for 3 hours. By gentle sidewise shaking, the sample was distributed at the specified temperature for constant weight. The drug sample was allowed to come to room temperature in a

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desiccator before weighing. The difference between successive weights should not be more than 0.5mg.

4.1.5 Melting point determination:
The melting point of active ingredients were determined by capillary method, by using definite quantity of active ingredients which were taken and placed in apparatus and melting point was determined and matched with standards.

4.1.7 Drug Content:
For Diclofenac Sodium:
Weigh accurately a Diclofenac sodium, shake with 70ml of Phosphate buffer 6.8 for 15 minutes, make up to 100ml with Phosphate buffer 6.8, and filter. Dilute 10ml of the filtrate to 100ml with Phosphate buffer 6.8. Further 10ml of the filtrate were make up to 100ml with Phosphate buffer 6.8 and measure the absorbance of the resulting solution at the maximum about 280nm.

For Misoprostol:
Misoprostol was accurately weighed and transferred into 100ml volumetric flask and dissolve in a water until clear solution is obtained. The resulting solutions was made to 100ml with 0.1N HCl and shake for 10 mins. The 10ml of the above solution was diluted up to 100ml with 0.1N HCl and filtered through 0.45µ membrane filter analyzed by UV/VIS double beam spectrometer at 237nm.

4.2 PREFORMULATION STUDIES:
It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

4.2.1 Drug–Excipients Interaction Study:
An infrared spectrum of pure drug, mixture of drug with each retardant and physical mixture of optimized formulation was recorded using FTIR Spectrophotometer. The scanning range was 500–4000 cm^{-1} and the IR spectra of samples were obtained using KBr disc method. Any change in spectrum pattern of drug due to presence of polymers was investigated to identify any chemical interaction.

4.2.2 Bulk density:
The bulk density also called as poured density. It is usually measured by passively filling in measuring vessel.

Procedure:
Pass the sample through 18 mesh to break the agglomerates that may formed during storage. Weigh the sample around 100gm and then fill the powder into a 250ml measuring vessel. Measure the volume (V_0).

$$\textbf{Bulk density } (\rho b) = M/V_0$$

Where,

M = Mass of the powder in gm
V_0 = Volume of the powder in ml

4.2.3 Tapped density:
The tapped density is the density measured by mechanically tapped measuring cylinder which contains materials in it. Tested by using tap density tester.

Procedure:
Weigh and fill the material into a cylinder, note the volume(V_0) and tap the material at the height of 14±2 with its own weight at the rate of 300 taps per min. Tap the cylinder 500 times initially, note the volume (V_a) and again tap the cylinder 750 times, note the volume(V_b). If difference between V_a and V_b is less than 2%, then stop the test and take V_b as the final volume (V_f) or if it is more than 2% again tap the cylinder 1250 times, note the volume (V_c) and take V_c as the final volume (V_f).

$$\textbf{Tapped density } (\rho t) = M/V_f$$

Where,
M = Mass of the powder in gm.
V_f = Final volume of the powder in ml.

4.2.4 Compressibility index or Carr's Index (CI):
It is useful to find out the powder flow indirectly. It is expressed in percentage and calculated by the formula mentioned below.

$$CI = \frac{(\rho t - \rho b)}{\rho t} \times 100$$

Where,
ρt = Tapped density of a powder.
ρb = Bulk density of a powder.

4.2.5 Hauser's ratio:
It is the measure of porosity of a powder to be compressed and also it's inter particulate interactions. The ideal range should be 1.2 to 1.5 and calculated by the formula mentioned below.

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$$HR = \rho t / \rho b$$

Where,
ρt = Tapped density of a powder.
ρb = Bulk density of a powder.

4.2.6 Angle of repose (θ):
It is a character related to inter particulate friction or resistance to movement between particles. It is to characterize the flow property of solids. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is determined by fixed funnel method and calculated by the formula mentioned below.

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

Where,
θ = Angle of repose in degrees
h = Height of the pile of powder in cm
r = Radius of the pile of powder in cm

4.2.7 Moisture content:
Take 2.5 to 3.5g of granules and observe the moisture content in moisture balance. Note the percentage of moisture content as displayed in the balance.

4.3 POST COMPRESSION STUDIES OF TABLETS:

4.3.1 Description:
The general appearance of a tablet including size, shape, colour, having score or not, coated or uncoated, should be observed. It is must to have a good appearance for consumer acceptance. Physical changes may occur during storage, which can be determined easily by matching with the description.

4.3.2 Weight variation:
Weigh individually 20 tablets, which were taken randomly and determine the average weight. Not more than 2 of the individual tablets weight should not deviate from the weight variation limits.

4.3.3 Thickness:
It can be dimensionally described & controlled. Thickness may affect the hardness, and dissolution rate. Tablet thickness can be measured by using callipers, and it should be measure at least for six tablets.

4.3.4 Diameter:
It is also dimensionally described & controlled. Tablet diameter can be measured by using dial calliper. It also should measure for six tablets in general.

4.3.5 Hardness:
Tablet requires certain amount of strength or hardness to withstand mechanical shocks occur during handling in manufacture, packing and shipping. Strength of the tablet was expressed as tensile strength (Kg/cm2). The tablet crushing load is the force, which is required to break a tablet. Six tablets have to take from each batch, and the average hardness has to be determined by using Monsanto hardness tester.

4.3.6 Friability:
Take few tablets of a weight as near as possible to 6.5 gm. Those tablets should be carefully de-dusted prior to testing. Accurately weigh the tablet sample and note the weight ($W_{initial}$) and place the tablets in the drum. Rotate the drum 100 times at 25±2 rpm and remove the tablets. Again de-dust the tablets as before and weigh accurately, note the value (W_{final}).

4.3.7 *In vitro* dissolution studies:
The study was carried out for 24 hours. 5ml of samples were withdrawn on time interval of 1,6 and 12th hour and replaced with fresh medium. Samples were filtered, diluted and absorbance was measured at 280 nm (Diclofenac) & 237 nm (Misoprostol) using UV-VIS Spectrophotometer.

Apparatus	**:**	USP Type II (Paddle type)
Medium	**:**	phosphate buffer 6.8 & 0.1 N HCl
Rpm	**:**	75
Volume :	900 ml	
Temp	**:**	37 ± 0.5ºC

4.3.8 Evalution of *invitro* release kinetics:
To study kinetics, data obtained from in vitro release were plotted in various kinetic models.

1. **Zero order equation: $C=K_0t$**
2. **First order equation: $\log C = \log C_0 - Kt/2.303$**
3. **Higuchi kinetics: $Q = Kt^{1/2}$**
4. **Hixson and Crowell erosion equation: $Q_0^{1/3} - Q_t^{1/3} = K_{HC}t$**

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5. **Korsmeyer – Peppas equation:** $M_t / M_\infty = Kt^n$

4.4 STABILITY STUDY:

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

V. RESULTS AND DISCUSSION:

5.1 RAW MATERIALS ANALYSIS:

S.NO	TEST	DICLOFENAC	MISOPROSTOL
1	**Color**	White to pale yellowish white	White color
2	**Odour**	Odourless	Odourless
3	**Taste**	Tasteless	Tasteless
4	**Solubility**	freely soluble in water, insoluble in Methanol.	freely soluble in ethanol.
5	**Melting Point**	280°C	210°C
6	**Loss On Drying**	0.43%	0.39%

Table No: 2 Raw Materials Analysis

5.1.1 Powder Derived Properties (Drug):

S.NO	DRUG	ANGLE OF REPOSE (Theta)	LOOSE BULK DENSITY (g/mL)	TAPPED BULK DENSITY (g/mL)	CARR'S INDEX (%)	HAUSNER'S RATIO
1	API (Diclofenac)	31.36	0.532	0.656	13.190	1.103
2	API (Misoprostol)	30.11	0.454	0.585	12.243	0.985

Table No: 3 Powder Derived Properties

5.1.2 Drug Content:

Linearity Of Diclofenac In Phosphate Buffer PH 6.8 (λ Max : 280nm)

S.NO	CONCENTRATION (µg / ml)	ABSORBANCE (nm)
1	10	0.072
2	20	0.123
3	30	0.179
4	40	0.245
5	50	0.295
6	60	0.353
7	70	0.429
8	80	0.478
9	90	0.531
10	100	0.575

Table No: 4 Linearity Of Diclofenac In Phosphate Buffer PH 6.8

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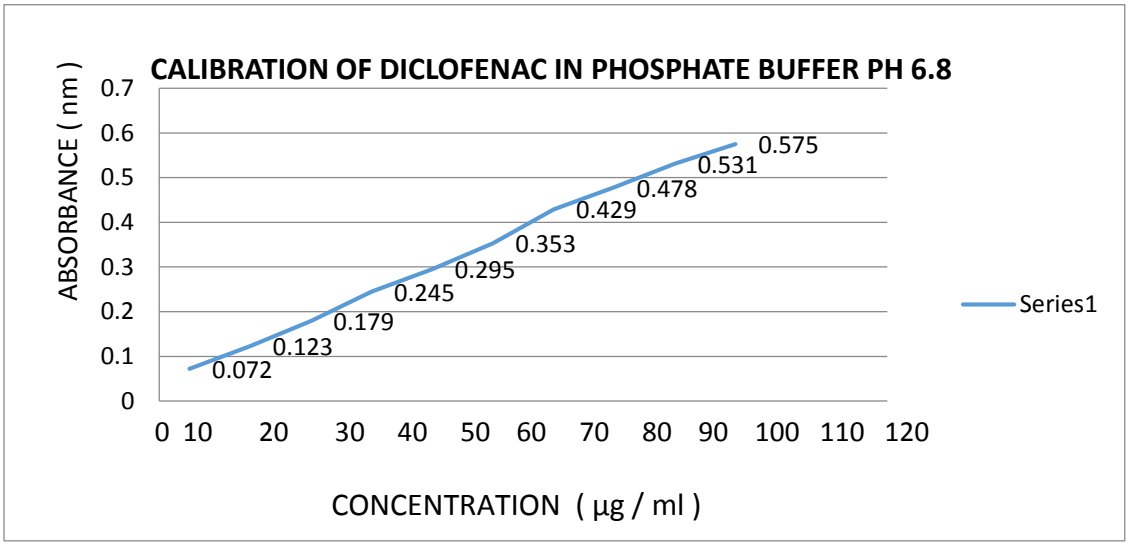

Figure No 6: Linearity Of Diclofenac

Linearity Of Misoprostol In 0.1N HCl (λ Max : 237nm)

S.NO	CONCENTRATION (µg / ml)	ABSORBANCE (nm)
1.	0	0.000
2.	2	0.086
3.	4	0.172
4.	6	0.278
5.	8	0.367
6.	10	0.472

Table No: 5 Linearity Of Misoprostol In 0.1N HCl

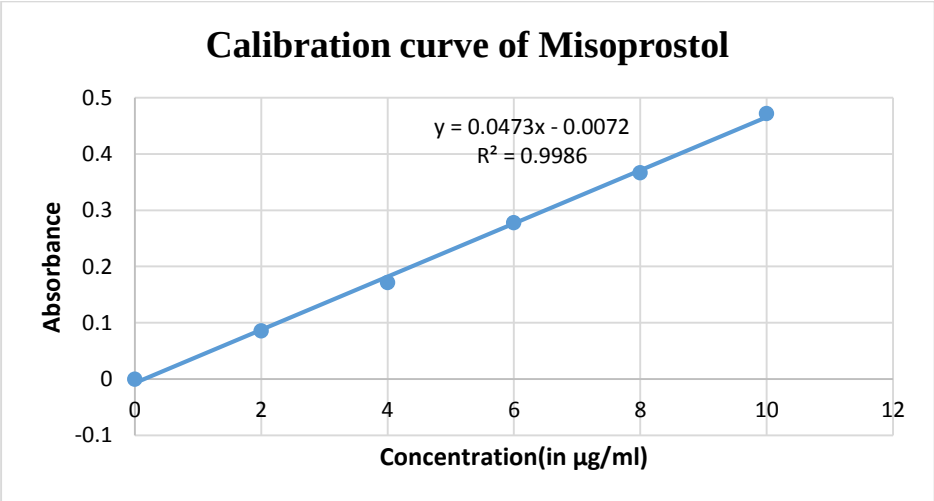

Figure No 7: Linearity Of Misoprostol

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5.2 PREFORMULATION STUDY:

5.2.1 Drug-Excipient Compatibility Studies:

S.No	DRUG & EXCIPIENTS	DESCRIPTION AT INITIAL DAY	RT, 40°C/75%RH in days		
			10th	20th	30th
1.	Diclofenac	White , crystalline powder	NC	NC	NC
2.	Misoprostol	White , crystalline powder	NC	NC	NC
3.	Microcrystalline Cellulose	White or almost white fine powder	NC	NC	NC
4.	CMC Sodium	White or almost white granular powder	NC	NC	NC
5.	Xantham Gum	Yellowish-white powder	NC	NC	NC
6.	Colloidal silicon dioxide	White or almost white granular powder	NC	NC	NC
7.	HPMC– K 100M	White or yellowish-white granular powder	NC	NC	NC
8.	Purified Talc	White or almost white greasy powder	NC	NC	NC
9.	Magnesium Stearate	White, fine, greasy powder	NC	NC	NC
10.	Sunset yellow lake	White, crystalline	NC	NC	NC
11.	Croscarmellose Sodium	Creamy white, hygroscopic powder	NC	NC	NC
12.	Crospovidone	White or yellowish-white hygroscopic powder	NC	NC	NC
13	HPMC E 15	White or yellowish-white granular powder	NC	NC	NC
14	Starch	White powder	NC	NC	NC

NC-No Change.

Table No: 6 Drug – Excipient Compatibility studies

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5.2.2 Pre-Compression Study Of Diclofenac:

F	BULK DENSITY	TAPPED DENSITY	COMPRESSIBILITY INDEX	HAUSER'S RATIO	ANGLE OF REPOSE	MOISTURE CONTENT
F_1	0.494±0.002	0.623±0.003	20.70±0.606	1.256±0.005	31°76´±0.01	3.16±0.01
F_2	0.486±0.002	0.618±0.004	21.35±0.185	1.266±0.005	32°76´±0.01	2.94±0.01
F_3	0.466±0.003	0.584±0.002	20.20±0.686	1.246±0.011	33°02´±0.02	3.76±0.02
F_4	0.474±0.002	0.598±0.002	20.73±0.310	1.256±0.005	33°20´±0.02	3.88±0.01
F_5	0.536±0.002	0.704±0.002	23.86±0.500	1.310±0.010	32°04´±0.02	3.40±0.02
F_6	0.547±0.001	0.714±0.002	23.38±0.355	1.300±0.010	32°03´±0.01	3.42±0.01

Table No: 7 Pre-Compression Study Of Diclofenac Granules

5.2.3 Pre-Compression Study Of Misoprostol:

F	BULK DENSITY	TAPPED DENSITY	COMPRESSIBILITY INDEX	HAUSER'S RATIO	ANGLE OF REPOSE	MOISTURE CONTENT
F_1	0.500±0.002	0.707±0.002	20.72±0.215	1.306±0.005	31°33´±0.01	3.49±0.02
F_2	0.544±0.002	0.711±0.001	22.10±0.391	1.220±0.010	30°70´±001	3.82±0.02
F_3	0.448±0.003	0.691±0.002	20.29±0.786	1.301±0.011	31°72´±0.01	2.91±0.01
F_4	0.567±0.002	0.532±0.002	20.78±0.530	1.284±0.008	31°11´±0.01	3.64±0.02
F_5	0.601±0.002	0.631±0.002	21.85±0.352	1.309±0.010	31°20´±0.02	3.91±0.02
F_6	0.531±0.001	0.644±0.002	23.44±0.398	1.333±0.010	31°03´±0.02	3.11±0.01

Table No: 8 Pre-Compression Study Of Misoprostol Granules

5.3 POST COMPRESSION STUDY:

F	WEIGHT VARIATION	HARDNESS	THICKNESS	FRIABILITY	DICLOFENAC DRUG CONTENT	MISOPROSTOL DRUG CONTENT
F_1	350.6±0.491	4.75±0.05	3.48±0.02	0.200±0.002	97.18±0.90	98.45±0.20
F_2	349.8±0.376	4.25±0.25	3.42±0.01	0.175±0.001	94.44±0.70	94.97±0.60
F_3	350.4±0.516	4.02±0.02	3.64±0.02	0.205±0.005	97.18±0.90	98.18±0.70
F_4	350.6±0.204	4.50±0.05	2.63±0.01	0.102±0.002	97.42±1.40	98.48±1.60
F_5	350.4±0.273	4.63±0.10	2.62±0.02	0.107±0.001	99.22±1.15	100.2±1.15
F_6	350.2±0.375	5.56 ±0.02	2.33±0.03	0.101±0.001	100.14±1.45	99.14±1.97

Table No: 9 Post-Compression Study Of Bilayer Tablets

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Figure No 8: Evaluation Of Bilayer Tablets

5.4 INVITRO DISSOLUTION STUDY:

- Dissolution test apparatus : Labindia
- Speed : 50 rpm
- Stirrer : Paddle type
- Volume of medium : 900 ml
- Volume withdrawn : 5 ml
- Medium used : pH 6.8 Phosphate buffer & 0.1N HCl
- Buffer temperature : 37 ± 0.5^0 C
- Diclofenac sodium : (λ Max : 280nm)
- Misoprostol : (λ Max : 237nm)

5.4.1 For Invitro Dissloution Study (DICLOFENAC SODIUM SR)

TIME IN HOURS	F1	F2	F3	F4	F5	F6
30 min	19.67±0.01	29.19±0.02	17.86±0.02	20.49±0.05	33.98±0.01	29.31±0.01
1th hour	24.32±0.01	34.98±0.01	29.57±0.01	32.43±0.01	40.77±0.01	39.87±0.01
4th hour	39.83±0.03	45.33±0.01	39.64±0.02	41.40±0.02	51.11±0.02	51.65±0.03
8th hour	65.83±0.03	75.39±0.03	55.64±0.02	69.43±0.02	80.82±0.02	75.65±0.03
16th hour	73.71±0.01	77.67±0.01	69.66±0.01	82.06±0.01	89.09±0.01	83.67±0.01
24th hour	95.20±0.05	93.94±0.02	85.03±0.01	91.07±0.03	96.24±0.04	98.92±0.02

*****Mean ± SD (n=3)

Table No: 10 Invitro Dissolution Study (Diclofenac sodium SR)

5.4.2 For Invitro Dissloution Study (MISOPROSTOL IR)

TIME IN MINS	F1	F2	F3	F4	F5	F6
5 min	19.56±0.01	18.43±0.02	22.07±0.01	18.02±0.02	21.07±0.01	21.78±0.02
10 min	41.78±0.01	34.65±0.02	41.16±0.02	29.71±0.03	33.16±0.01	43.66±0.01
20 min	60.89±0.02	79.87±0.03	62.97±0.01	41.91±0.01	50.05±0.03	58.13±0.02
40 min	79.72±0.01	90.52±0.02	77.58±0.03	60.56±0.01	71.44±0.02	66.56±0.01
60 min	92.32±0.01	-	88.63±0.02	78.89±0.01	85.56±0.02	78.05±0.01

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75 min	-	-	-	89.58±0.03	98.12±0.01	99.31±0.03

Table No: 11 Invitro Dissolution Study (Misoprostol IR)

Discussion:

The *In vitro* dissolution release profile of various formulations was studied. The results of *in vitro* dissolution studies of Sustained release formulations, observed that the formulation F6 having a release profile up to 24 hours and Immediate release formulations, observed that the formulation F6 having a release profile up to 75 mins. It was selected for formulation of sustained release tablet among from formulations F1 to F6. Concluded that the drug release from tablet by the combination of polymers HPMC K_{100}M, Sodium Caroboxymethylcellulose and Guar Gum shows the better release rate profile. Release time also increases with polymer concentration also increased. HPMC K_{100} M along with xantham Gum, microcrystalline cellulose shows the release up to 24 hours.

5.5 HPLC ANALYSIS:

MOBILE PHASE	**WATER: METHANOL: ACETONITRILE (10:60:30)**
Wavelength	279 nm
Flow rate	0.6 ml/ min.
Run time	10 min.
Column	C-18, V size

Table No: 12 Mobile Phase

S.NO	**NAME**	**RT**
1	Diclofenac	2.37
2	Misoprostol	4.37

Table No: 13 HPLC Data

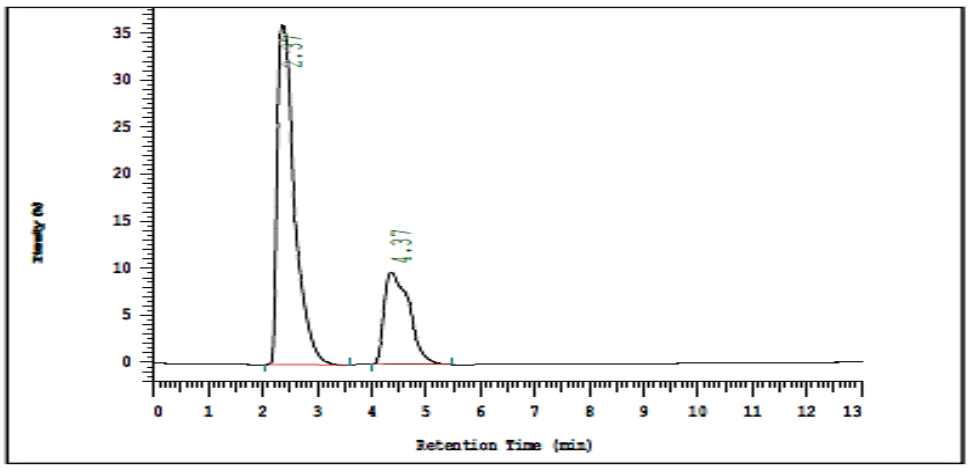

Figure No 9: HPLC Analysis

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5.6 SPECTRUM FT-IR STUDY:

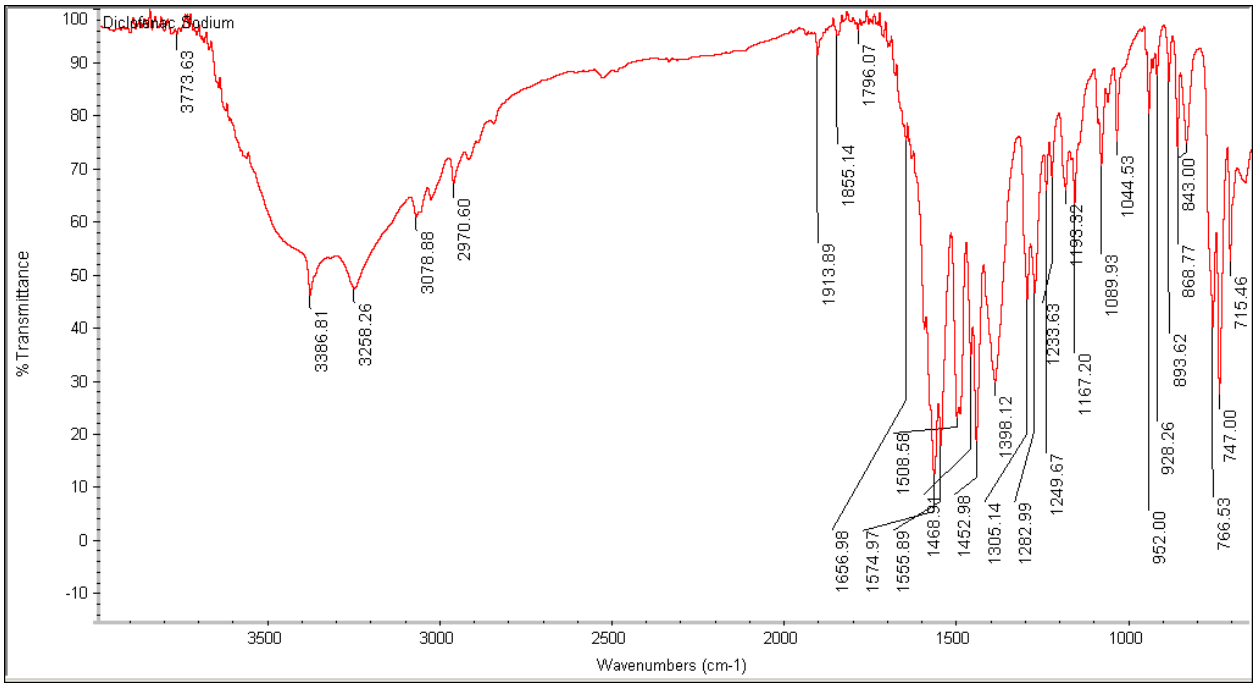

Figure No: 10 IR Spectrum Of Diclofenac (Formulation 6)

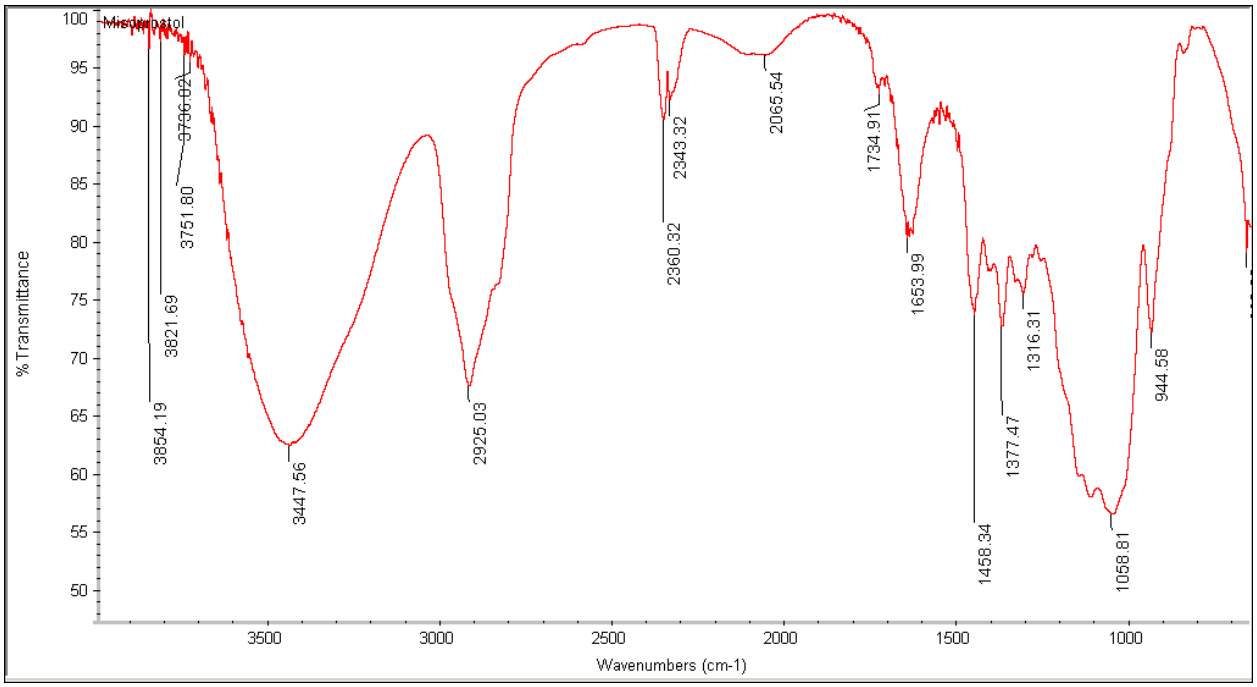

Figure No: 11 IR Spectrum Of Misoprostol (Formulation 6)

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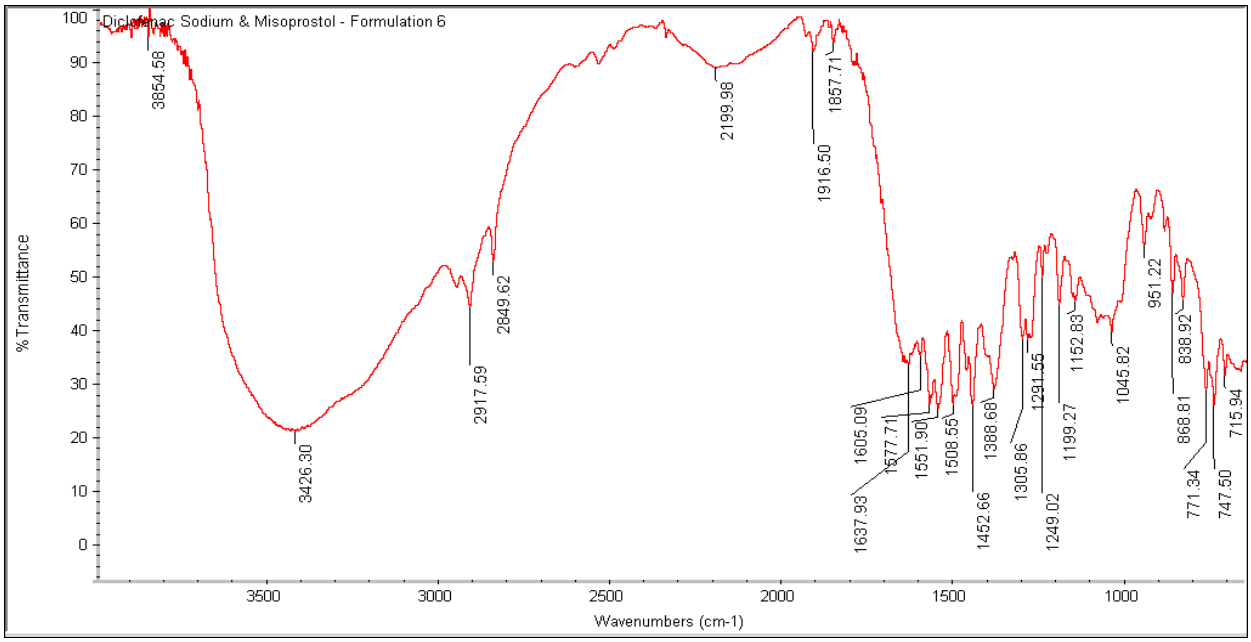

Figure No: 12 IR Spectrum Of Diclofenac & Misoprostol (Formulation 6)

5.7 PHARMACOKINETIC PARAMETER:

Data analysis:

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model using Kinet DS 3.0 software. Based on the r-value, the best-fit model was selected.

DRUG RELEASE BILAYER TABLET (Best formulation)	ZERO ORDER	FIRST ORDER	HIGUCHI KINETICS	PEPPAS KORSMEYER	HIXSON CROWELL
F6	0.9800	0.4157	2.0892	0.9993	0.7173

Table No: 14 Drug Kinetics Release (Diclofenac SR & Misoprostol IR) F6

5.8 STABILITY STUDIES:

Parameters	1st Month		2ndMonth		3rdMonth	
	RT	40^0C	RT	40^0C	RT	40^0C
Uniformity of Weight**	350.55±1.52	350.45±1.23	350.45±1.23	350.54±2.12	350.45±1.23	350.54±2.12
Thickness*	3.48±0.087	3.38±0.076	3.38±0.099	3.40±0.191	3.38±0.076	3.35±0.191
Friability*	0.12±0.034	0.12±0.044	0.12±0.065	0.13±0.298	0.12±0.044	0.13±0.298

Table No: 15 Stability Study at 40 ° C / 75% RH

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Intervals in Months RT	% Drug content*		% Cumulative Release *	
	RT	40°C	RT	40°C
1st month	99.31±0.06	100.98±0.789	97.41±.94	97.86±0.43
2nd month	99.01±0.06	99.31±0.06	97.39±0.809	97.28±1.490
3rd month	98.98±0.05	99.31±0.06	97.48±1.43	97.41±1.394

*Mean ± SD (n=6)

Table No: 16 Tablet at Stability Study at 40 ° C / 75% RH, Assay and Dissolution Profile

VI. SUMMARY AND CONCLUSION:

The Current research study focused towards the development of **Diclofenac and Misoprostol bilayer tablet.**

In formulation matrix system was based on swellable polymer which is essential for sustaining the drug release pattern. HPMC, Xantham Gum and Sodium Caroboxymethylcellulose helps to get the predetermined release profile over a period for 24 hours. Various types of sustained release (SR) batches were formulated by wet granulation technique.

The formulations were evaluated for physical chemical characteristics, in vitro dissolution study and stability study. Below the conclusions have been made from the present study method.

- Prospect of **Drug – Excipients interaction** was investigated by FTIR of analytical method.
- **Physical characteristics** of all the blended formulations were adequate.
- Primed tablets evaluated for **assay, weight variation, hardness and thickness** were found to be within the official monograph limits.
- Tablet ***In Vitro* Dissolution study of SR formulations F6** showed release profile for 24 hours which complies with USP at a certain concentration of $HPMCK_{100}$ when compared with other 5 formulations.
- **Stability studies** were conducted for 3 months at room temperature and 40°C/75% RH. After the duration, the product was analysed for physical appearance, dissolution study and assay profile. We got the results were found to be within the predetermined specification limits.
- The formulated SR tablets containing of Diclofenac and misoprostol were found to be stable nature. Hence, to reduce the frequency of administration and to improve the patient compliance, SR tablets were successfully formulated and evaluated.

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