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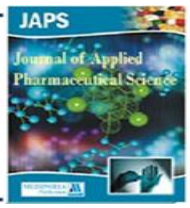

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Formulation and Evaluation of Bilayer Tablets of Diclofrenac Sodium with Ranitidine HCL for Sustained and Immediate Release

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ABSTRACT

The aim of present study is to formulate and evaluate the bilayered tablets containing Diclofenac Sodium in the sustained release (SR) portion and Ranitidine HCl in the immediate release (IR) portion in order to produce a single tablet containing two different classes of drugs as widely prescribed by doctors and to have better patient compliance.The sustained release layer of Diclofenac Sodium was prepared by using different grades of HPMC like, HPMC E15, HPMC K4M, K100M, and Ethyl Cellulose with cross carmellose along with other excipients like Magnesium stearate, Microcrystalline cellulose & PVP by wet granulation technique. The Immediate release layer of Ranitidine Hcl was prepared by direct compression Method. The powders were evaluated for their flow properties and the finished tablets were evaluated for their physical parameters. The drug release study of Ranitidine HCl and Diclofenac Sodium were evaluated using USP-XXII paddle type dissolution apparatus. The release rate of Ranitidine HCl was studied for 45 min using water as media and that of Diclofenac Sodium was studied for 2 h in 1.2pH buffer followed by 6 h in pH 6.8 phosphate buffer media using a developed HPLC method. The release rate of ranitidine HCl from all the formulations was more than 80% at 45 min. In case of HPMC E15, HPMC K4M, K100M based tablets with the increasing of polymer content the release mechanism moved to super case. Total four trial batches of each drug have been manufactured to optimize and develop a robust and stable formulation, the stability studies of the products also comply with ICH guidelines.

Keywords: Bilayer tablets, Diclofenac Sodium, Ranitidine Hcl, HPMC, Sustained release, Wet granulation, Direct compression.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly, and then maintain the desired drug concentration. (Artuhr *et al.,* 1999). 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. Diclofenac (Arancibia *et al.*, 1999) is an acetic acid nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. Diclofenac is used to treat pain, menstrual pain, dysmenorrhea, ocular inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and actinic keratosis.

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.

Ranitidine hydrochloride (Katzung *et al.,* 2004) is H2-receptor blocker. It reduces acid secretion stimulated by histamine as well as gastrin and cholinomimetic agents. It is widely prescribed in a active duodenal ulcers, gastric ulcers, gastro esophageal reflux disease and erosive esophagitis. The recommended adult oral dosage of ranitidine is 150mg twice daily or 300mg once daily.

NSAIDs like Diclofenac Sodium are widely used for the treatment of musculoskeletal pain. 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 (Silverstein *et al.,* 2000). It is not widely appreciated that NSAIDs can also cause serious lower gastrointestinal complications, including bleeding, perforation, stricture, anemia and hypoalbuminemia. Although the reported incidence of NSAID related lower gastrointestinal complications varies from 14% to 40%, the true incidence is uncertain because patients and doctors often do not realize that there is a problem (Lanas *et al.,* 2005, Laine *et al.,* 2003). 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) in the sustained release portion and a H2 blocker (Ranitidine Hcl) in the immediate release portion in order to reduce the incidence of NSAID-induced gastrointestimal injury which may be occurred by not taking anti-ulcerant along with NSAID in case of chronic pain (Medscape Today , 2008).

The objective of present study is to prepare a bilayer tablets of Diclofenac Sodium (SR) and Ranitidine Hcl (IR) by using different grades of HPMC like, HPMC E15, HPMC K4M, K100M, and Ethyl Cellulose with cross carmellose along with other excipients by combination of both wet granulation and direct compression methods. To evaluate granular blends in terms of Angle of repose, Bulk and tapped density, Carr's index, Hausner's Ratio and to evaluateBi-layer matrix tablets interms of hardness, weight variation, friability, thickness, drug content uniformity, In vitro dissolution studies in 1.2 and 6.8 pH.

MATERIALS AND METHODS

Materials

Ranitidine Hcl and Diclofenac Sodium was a gift sample obtained from M/s. Medley Pharmaceuticals Ltd., Daman and all other excipients such as Avicel pH-102, Pregelatinized Starch, HPMC E15, HPMC K4M, Ethyl Cellulose MCC, PVPK30, Aerosil,Talc and Magensium Stearate , were procured from M/s. Yarrow Chem Products., Mumbai, India. All other chemicals/reagents used were of analytical grade.

Potency Calculation of Active Pharmaceutical Ingredients

$$\text{Potency} = \frac{\text{label claim}}{\text{Effective assay}} \times 100 \times \frac{\text{Actual quantity of Active drug required per tablet}}{100 - \text{water content}} \times 100$$

METHODS

Analytical Methods

UV Spectroscopy

For Ranitidine Hcl

100 mg of Ranitidine Hcl was weighed accurately and transferred it to 100 ml volumetric flask. Dissolved it in 0.1N Hcl and 6.8 pH Buffer and make up the volume up to 100 ml with respective solvent. This was considered as stock solution (1000 mcg/ml). further dilutions were made with this stock solution and scanned in the range of 400-200 nm using respective blank in UV spectrophotometer. (IP, 1996).

For Diclofenac Sodium

Stock Solution (1000 µg/ml): 100 mg of Diclofenac Sodium was weighed accurately and transferred it 100 ml volumetric flask. Dissolved it in Methanol, 1.2 pH Buffer, 6.8 pH buffer and make up to the volume up to 100 ml with respective solvent. (IP, 1996).

FTIR Spectroscopy

The drug-excipients interaction studies were carried out to check the physical and chemical interaction of materials that could occur in presence of other. The drug-excipients interaction was studied by FTIR spectroscopy by KBr pellet method. Sample for analysis and KBr were taken in 1:100 ratio and ground in motor for even distribution of sample in KBr. The pellet was prepared in the form of disk by applying pressure of 5 tons for 5min using hydraulic press and subjected to FTIR. The wave number range of 400-4000cm^{-1}. (Indop *et al.,* 2002).

Preparation of Ranitidine Hcl Blend by Dry granulation Method

- Weighed all the ingredients as per the quantities defined in Table No.1
- Passed all the ingredients through appropriate sieves such as #22, #40, # 60 & #80 mesh and collected the individual materials in separate poly bags.
- Mixed measured quantity of Ranitidine Hcl and Avicel pH-102 geometrically then added PVP-K30 and Pregelatinized Starch to it and blend for 10 min.
- Added Aerosil to the above step (3) and blended for 20 min.
- Added Magensiun stearate to the above step (4) and blended for 5 min.

- Compressed final blend by using double rotary, D- tooling, bilayer compression machine using 12 mm round shaped punches and corresponding dies.
- Formulation code for the final blend is marked as FR-I and for bilayer Tablets as TF1, TF2, TF3, TF4, TF5, and TF6.

Table. 1: Composition of Granules for Ranitidine Hcl - Immediate Release Layer.

Sr. No.	Ingredients	Quantity Per 10 Tablets (in mg)
	Formulation Code : FG-I	
1	Ranitidine Hcl	1500.00
2	MCC (Avicel pH-102)	640.00
3	PVP-K30	30.00
4	Pregelatinized Starch (Starch 1500)	550.00
5	Aerosil 200	20.00
6	Magnesium Stearate	10.00
	Total	2750.00

Preparation of Diclofenac Sodium Blend by Wet Granulation Method

- Weighed all the ingredients as per the quantities defined in Table No.2
- Passed all the ingredients through appropriate sieves such as #40, # 60 & #80 mesh and collected the individual materials in separate poly bags.
- Prepared binder solution by dissolving PVPK30 in purified water.
- Mixed all the materials except lubricants for 25 min.
- Added binder solution to the above step (4) and mixed until uniform dough mass granules are formed.
- Dried the granules in FBD at 50-55°C temperature till LOD of the granules reaches to 1.5 – 2%.
- Passed the dried granules through #16 mesh.
- Transferred all the sifted granules to the blender and lubricants were added except Mg.stearate and blended for 5 min.
- Added magnesium stearate to the above step (8) and mixed for 2 min.
- 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 FD-I, FD-II, FD-III, and FD-IV and for bilayer Tablets as TF1, TF2, TF3, and TF4.

Evaluation of Granules

To assess physicochemical properties and release characteristics of the granular blend, all formulations are subjected to pre-formulation studies like bulk density, tapped density, Angle of repose, compressibility index, Hausner's ratio and particle size distribution as shown in Table. No. 3 and 4. (Sarfarz *et al.*, 2004).

Table. 2: Composition of Granules for Diclofenac Sodium - Sustained Release Layer.

Sr.No.	Ingredients	Formulation Code			
		FM-I	FM-II	FM-III	FM-IV
		Quantity per 10 Tablets (in mg)			
1	Diclofenac Sodium	1000	1000	1000	1000
2	HPMC E-15	500	--	--	150
3	Ethyl Cellulose	--	500	--	--
4	HPMC K4M	--	--	500	500
5	PVP K- 30	150	150	150	150
6	Micrcrystalline Cellulose	520	520	520	370
7	Aerosil	20	20	20	20
8	Talc	20	20	20	20
9	Magnesium sterate	40	40	40	40
10	Purified Water	Q.S.	Q.S.	Q.S.	Q.S.
	Total	2250	2250	2250	2250

Table. 3: Evaluation of Granules of Diclofenac Sustained Release Layer.

Formulation Code	Parameters				
	Angle of repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio
DF-I	27.59	0.50	0.57	14.00	1.14
DF-II	25.65	0.46	0.54	17.39	1.17
DF-III	26.46	0.45	0.56	24.44	1.24
DF-IV	27.74	0.56	0.64	14.28	1.14

Table. 4: Evaluation of Granules of Ranitidine Immediate Release Layer.

Formulation Code	Parameters				
	Angle of repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio
RF-I	25.25	0.46	0.54	17.39	1.17

Table. 5: Evaluation of Parameters of Bilayer Tablets of Ranitidine IR and Diclofenac SR.

Formulation Code	Hardness (kg/cm^2)	Friability (% w/w)	Weight Variation (mg)	Thickness (mm)
TF 1	5.9	0.36	504 ±0.07	3.1
TF 2	5.5	0.42	507 ± 0.01	2.9
TF 3	5.7	0.39	493 ± 0.04	3.0
TF 4	6.1	0.41	495 ± 0.03	2.9

Angle of Repose

This is the maximum angle possible between the surface of a pile of granules and the horizontal plane.

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

Where, θ = angle of repose

h = height of the heap

r = radius of the heap

Particle size distribution of granules

The particle size distribution was measured using sieve analysis method.

Bulk Density (BD) & Tapped Density (TD) of granules

The bulk density and tapped bulk density were determined and calculated by the following formulas.

BD = weight of the powder / initial volume

TD = weight of the powder / final volume

Compressibility of granules

The compressibility index was determined by Carr's compressibility index and Hausner's ratio..

Carr's index = TD – BD X 100 / BD

Hausner's ratio: Hausner's ratio = TD / BD

Evaluation of Compressed Tablets: (Lachmen *et al.*, 1987)

The prepared tablets were evaluated for weight variation, disintegration test, dissolution test, thickness, hardness uniformity of dosage units and friability.

The weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2. The hardness of 6 tablets was determined using the Monsanto hardness tester.

The Friability was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated.

The thickness of the each 10 tablets was measured with the Varnier Caliper.

The Uniformity of dosage units is assessed according to the USP requirements for content uniformity. The batch meets the USP requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to115% of the label claim and the RSD is less than or equal to 6%. According to the USP criteria, if one of these conditions is not met, an additional 20 tablets need to be tested. Not more that 1 unit of the 30 tested should be outside the range of 85% and 115% of the label claim and no unit outside the range of 75% to 125% of label claim. For all RSD should not exceed 7.8%. The Disintegration test for immediate release layer is determined using the disintegration test apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000 ml of purified water maintained at 37 ±2°C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

***In- vitro D*rug Release (**Chakraborty *et al.*, 2008)

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 24 hrs period for Diclofenac Sodium SR and 1 hr for Ranitidine Hcl IR , using an automated paddle dissolution system. A minimum of 6 tablets per batch were tested.

The media used was 0.1N HCl at a pH 2.0 and a volume of 750 ml for the first 2 hours after which 250 ml of 0.2 M sodium phosphate, tribasic, was added to give a final pH of 6.8 and maintained at 37+ 0.5◦C. Test sample (5ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using UV (ultraviolet) spectrophotometer at λmax 270,280,290 nm for Diclofenac Sodium (Umarkar et al ., 2005) and 315 & 228 nm for Ranitidine Hcl. **(**Natasha *et al.*, 2011)

The evaluation results of the different tablet formulations are shown in Table No.5, 6 and 7.

Stability Studies (ICH Geneva 2003)

The optimized formulation was subjected for two month stability study according to ICH guidelines**.** The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were then stored at Room Temperature 40ºC / 75% RH for 2 months and evaluated for their permeation study.

RESULTS AND DISCUSSION

UV Spectroscopy

The UV absorption of 10 µg/ mlin 0.1N Hcl (pH-1.2) in the range of 200-400 nm exhibit maximum at 315 & 228 nm in case of Ranitidine HCl and at 270 , 280 & 290 nm in case of Diclofenac Sodium.

FTIR Spectroscopy

IR Spectra of pure drugs (Ranitidine & Diclofenac) was carried out for qualitative compound identification. The IR spectrum of Ranitidine hydrochloride shows that characteristic peak at 2500cm-1 (Characteristic peak for N+-H bond in protonated tertiary amine group), 1610cm-1 (Stretching vibration of C=N in aci-nitro group of nitronic acid), 1460cm-1 & 1252cm-1 (Stretching vibration of nitro group attached to saturated carbon) where as the IR spectrum of Diclofenac Sodium is characterized by presence of NH, OH, CH (aromatic hydrogen) stretching's, at 3400cm^{-1}, 3500 cm^{-1}, 3050 cm^{-1} respectively. The C=C stretching of benzene is found at 1200-1600 cm^{-1},the C-H stretching is found at 2950 cm^{-1} and carbonyl group at 1700 cm^{-1} . The individual and comparative graphs are as shown in Figure 1.

Table. 6: Evaluation *of in- vitro* Drug Dissolution Profile of Different Bilayer Formulations.

Sr.No.	Test	Specification	PERCENT DRUG RELEASE			
			TF 1	TF 2	TF 3	TF 4
1	**Ranitidine Hcl**					
	0 min	NLT 85% of	0	0	0	0
	10 min	the labeled	90	89	90	90
	15 min	amount	92	91	92	92
	30 min	dissolved in 45	95	95	95	95
	45 min	min	99	98	99	99
2	**Diclofenac Sodium**					
	0 Hr		0	0	0	0
	1st Hr		67.31	59.45	51.67	35.33
	4th Hr		84.56	81.34	75.12	65.98
	8th Hr		95.09	92.76.	86.79	89.12
	12th hr		100.9	99.52	100.01	102.20

Table. 7: Evaluation of Assay profile of Different Bilayer formulations.

Sr.No.	Test	Specification	PERCENT DRUG RELEASE			
			TF 1	TF 2	TF 3	TF 4
1	Ranitidine Hcl	90 - 110%	100.4	99.5	101.1	101.4
2	Diclofenac Sodium	of the labeled amount	99.5	99.7	99.6	99.9

Table. 8: Evaluation *of In- vitro* Drug Dissolution and Assay Profile of Bilayer Tablets of Stability Batch (TF4).

Sr.No.	Test	Specification	CUMULATIVE PERCENT DRUG RELEASE		
			Initial Results	1st Month Results	2nd Month Results
1	**Ranitidine Hcl**				
		NLT 85% of the labeled amount dissolved in 45 min	100.7	99.3	99.5
2	**Diclofenac Sodium**				
		1st Hr	33	29	31
		4th Hr	67	73	69
		8th Hr	87	91	89
		12th hr	101	99	100
		ASSAY			
1	**Ranitidine Hcl**	95 - 110% of the labeled amount	100.7	100.2	100.7

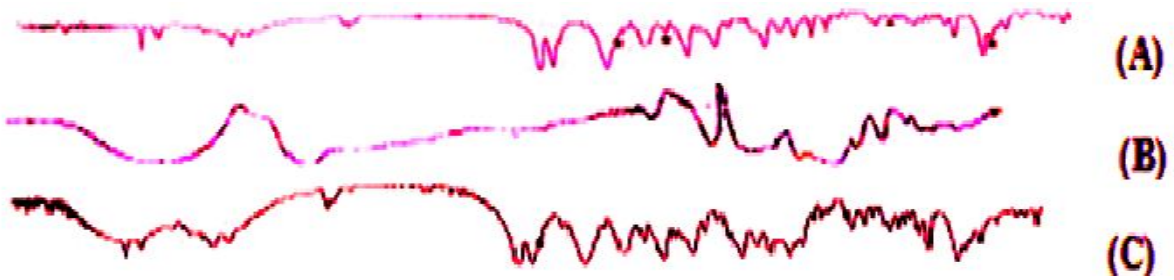

Fig. 1: F.T.I.R. Spectra of (A) Pure Ranitidine Hcl, (B) Pure Diclofenac Sodium and (C) Bilayer Tablet of Best Formulation - TF-IV.

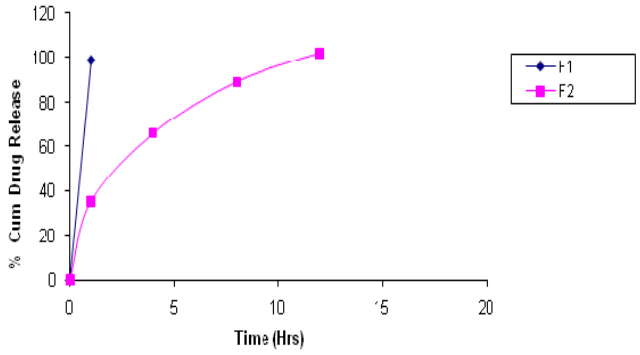

Fig. 2: Plot of Ranitidine Hcl IR Layer and Diclofenac Sodium SR Layer for Bilayer Tablet of Best Formulation TF4.

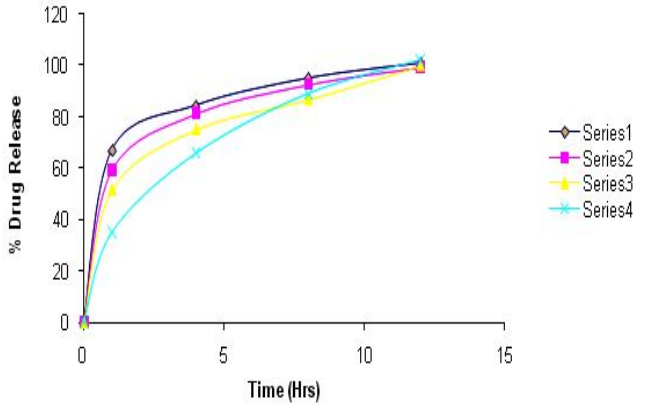

Fig. 3: Plot of Different formulations of Diclofenac Sodium SR Layer (DF-I to DF-IV).

Evaluation of Blend

The micromeritic properties such as of bulk density, tapped density, Angle of repose, compressibility index, Hausner's ratio and particle size distribution of Ranitidine Hcl immediate release layer blend and Diclofenac Sodium sustained release layer were studied. The overall results were shown in Table No. 3 and 4. The value of bulk density indicates good packing characteristics. The compressibility index of the formulation found to be below 15 indicating excellent flow properties of granules which were further confirmed by determining the angle of repose, it is in the range of 25° to 27° which indicates good flow properties.

Evaluation of Tablets

The compressed Tablets were evaluated for weight variation, thickness, hardness uniformity of dosage units and friability. The results of all the 7 formulations (TF1 to TF4) are shown in Table No.5

The drug content of the tablets was assayed by HPLC. The assay results of all the 4 formulations (TF1 to TF4) are shown in Table No. 7

***In vitro* Dissolution Study**

The *in-vitro* dissolution characteristics of Ranitidine Hcl and Diclofenac Sodium bilayer tablets are shown Table No.6.

Based on the *in-vitro* release profile of drug formulations of TF1 to TF4, the formulation TF4 showed better drug release, which was achieved by increasing the polymer concentration by combining two polymers such as HPMC K-4M and by adding HPMC 15cps which release the drug in a controlled rate at regular time intervals in appropriate concentrations as per the limits. Hence formulation TF4 was selected for further stability studies.

Stability Studies

The selected formulation TF4 was subjected to accelerated stability studies for 60 days at Room Temperature 40^0C / 75% RH, *in vitro* permeation study was performed on every week and showed negligible change in permeation profile. The formulation subjected for stability studies was found to have no change in the physical appearance and drug content as shown in Table No.8

CONCLUSION

The present study was carried out to prove that a bilyaer tablet of Ranitidine Hcl as IR layer and Diclofenac Sodium as SR layer can be formulated. HPMC-K4M, Ethyl Cellulose & HPMC 15cps are used for sustaining the layer of Diclofenac Sodium individually and/or in combination of any two. The system provides zero order and near zero order release. This concept also explains the applications of IR/SR from single dosage form which results in cost effectiveness and reduces the symptoms of Ulcer, which is major side effect caused by Diclofenac Sodium by fixed dose combination of Diclofenac Sodium with Ranitidine Hcl.

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