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FORMULATION AND *IN-VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS FOR VALDECOXIB

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ABSTRACT

Purpose: The ultimate aim of this current study was to design of sustained release matrix tablets for valdecoxib.

Methodology: SR matrix tablets of were formulated by using wet granulation technique with different polymers. The formulated SR matrix tablets are evaluated by characterization of flow properties like angle of repose, bulk density, compressibility index, hausner's ratio and characterization of physiochemical properties such as thickness, diameter, weight variation test, hardness, friability, drug content, *in vitro* drug release studies. Drug-polymers interaction was predicted by FT/IR Spectroscopy and DSC method.

Results: The SR matrix tablets were formulated and evaluated for flow properties, physiochemical characterization of matrix tablets, *in vitro* drug release studies. The *in vitro* dissolution studies revealed that the release patterns of the VC8 containing HPMC K100M and ethyl cellulose were probably showing maximum retardation of drug release and it shows super case-II transport, for these reasons, it was considered that the formulation VC8 as best formulation among all the nine formulations.

Conclusion: The results encourage a potential use of SR matrix tablet to prolong the dissolution rate and hence its improvement in treatment efficacy and patient compliances through oral route.

Keywords: HPMC K100M, ethyl cellulose, microcrystalline cellulose, PVP K30, valdecoxib

INTRODUCTION

Over past 30year as the expanse and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist **[1-2]**. The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery **[3-4]**. In recent year sustained release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release technology is relatively cow field and as a consequence, research in the field has been extremely fertile and has produced many discoveries **[5-6]**.

Valdecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is classified as a nonsteroidal anti-inflammatory drug (NSAID). Valdecoxib is used for its anti-inflammatory, analgesic, and antipyretic activities in the management of osteoarthritis (OA) and for the treatment of dysmenorrhea or acute pain. Unlike celecoxib, valdecoxib lacks a succinimides chain and does not require CYP450 enzymes for metabolism **[7-8]**.

MATERIALS & METHODS

Materials

Valdecoxib was obtained as a gift sample from Sunglow pharmaceuticals, Puducherry. HPMC K100M, ethyl cellulose were obtained from Tristar formulations Pvt. Ltd., Puducherry. Microcrystalline cellulose was gifted by Lobachemie Pvt. Ltd., Mumbai. PVPK30 was gifted by Gift sample from Nickon laboratories Pvt. Ltd., Puducherry.

Methods

Formulation and Preparation of SR Matrix Tablets

All the ingredients mentioned in **Table 1** were preweighed and passed through mesh #60 separately. The composition of 75 mg valdecoxib of the drug: polymer ratio (HPMC K100M, Ethyl cellulose) and filler microcrystalline cellulose (MCC) were dry mixed thoroughly for 10 minutes. The binder preparation was done in non aqueous medium taken poly vinyl pyrolidine K 30 dissolved in isopropyl

alcohol. The wet mass was prepared by adding sufficient quantity of solvent. Both the masses drug polymer mass and binder preparation was mixed and the obtained wet mass was passed through sieve #8 to get granules. The granules were dried and passed through sieve #24 and used for evaluation of flow characteristics **[9-10]**.

Table 1: Composition of valdecoxib SR matrix tablet

Ingredients(mg)	VC1	VC2	VC3	VC4	VC5	VC6	VC7	VC8	VC9
valdecoxib	75	75	75	75	75	75	75	75	75
HPMC K100M	37.5	75	112.5	-	-	-	18.75	37.5	56.25
Ethyl cellulose	-	-	-	37.5	75	112.5	18.75	37.5	56.25
Microcrystalline cellulose	80.9	48.2	5.7	80.9	48.2	5.7	80.9	48.2	5.7
Polyvinyl pyrrolidone-k30	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Total weight	200	200	200	200	200	200	200	200	200

All the quantities are expressed as mg per tablet

Drug Excipient Compatibility Studies [11-12]

To study the valdecoxib compatibility with different formulation excipients Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC) was done. FTIR, DSC studies are performed on samples of valdecoxib pure drug(A), solid admixture of valdecoxib +HPMC K100M(B), valdecoxib +ethyl cellulose(C), valdecoxib +HPMC K100 +Ethyl cellulose(D).

The IR Spectra of the test samples were obtained using KBR disk method. About 2-3 mg of samples were mixed with dried IR grade KBr powder and the spectra were obtained using FTIR spectrophotometer in between the wave number range of 4000-400cm-1.DSC studies were performed using a DSC (diamod, Mettler star) with thermal analysis data system, computer, and a plotter interface. Indium/zinc standards were used to calibrate the temperature and enthalpy scale. Accurately weighed 5-6 mg samples were hermetically sealed in aluminum pans and heated at constant rate of 10°C/min over a temperature range of 40 to 300°C and inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50ml/min.

Evaluation of Granules [13-14]

The angle of repose was measured by using funnel method, which indicates the flowability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= weight of the powder / volume of the packing. TBD= weight of the powder / tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100.The physical properties of granules were shown in **Table 2**.

Evaluation of SR matrix Tablets [15-16]

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods shown in **Table 3**.

Drug Content [17]

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 75 mg of valdecoxib was transferred into a100 ml standard volumetric flask. Then added 50ml of pH 7.4 phosphate buffer solution. It was gently shaken for 15 minutes. Then made upto the mark with pH 7.4 phosphate buffer solution. The solution was filtered through a whatmann filter paper, diluted suitably and the absorbance of resultant solution was measured by using Elico-SL 159 UV-Visible spectrophotometer at 290.5 nm using pH 7.4 phosphate buffer as blank.

***in vitro* Drug Release Study [18-19]**

The release rate of valdecoxib from matrix tablets was determined using United States Pharmacopoeia dissolution testing apparatus I (Basket method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed at 50 rpm using 900 ml of pH 1.2 for the first 2 hrs and phosphate buffer pH 6.8 from 2-12 hrs at 37 ± 0.5°C. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted suitably. Absorbance of these solutions was measured at 292.5 nm using Elico-SL 159 UV-Visible spectrophotometer. For each formulation, the experiments were carried out in triplicate.

RESULTS AND DISCUSSION

Drug-excipient compatibility studies

Figure 1 (A, B, C, D) shows the FTIR spectra of pure valdecoxib,valdecoxib +HPMC K100M, valdecoxib +ethyl cellulose, valdecoxib +HPMC K100 +Ethyl cellulose, respectively. The spectrum of pure valdecoxib shows some characteristic peaks at 1588.85 cm-1 due to C=O stretching, 3268.70 due to a C-H stretching,1486.33 due to C-C stretching, 3372.42 due to stretching vibration of O-H bond. The physical mixtures of drug with polymers also showed similar peaks at the above wave numbers. DSC was performed to characterize thermal changes the melting behaviour of losartan potassium with other excipients present in different formulations. **Figure 2 (A, B, C, D)** depicts the thermograms of heat verses temperature for pure valdecoxib solid admixture of valdecoxib +HPMC K100M, valdecoxib +ethyl cellulose, valdecoxib +HPMC K100 +Ethyl cellulose respectively. The prominen and sharp endothermic peak at 1616.66°C.

G Characterization of Powder Blend

Granules prepared for compression of

controlled release tablets were evaluated for their flow properties, the results were shown in **Table 3**.

Physicochemical Evaluation of Sustained Release Tablets

Table 4 indicates the results of physicochemical properties (hardness, thickness, weight variation, friability and assay).

***In vitro* drug release**

The drug released from formulation VC1 to VC3 containing HPMC K100M were found to be 93.90 ± 0.83, 90.55 ± 1.55, and 90.14 ± 01.33 % for valdecoxib. The drug released from formulation VC4 to VC6 containing ethyl cellulose were found to be 95.28 ± 2.07, 97.30 ± 0.06and 92.02. ± 0.79% for valdecoxib. The drug released from formulation VC7 to VC9 containing both HPMCK100M and ethyl cellulose were found to be 90.29 ± 1.31, 80.23 ± 1.42 and 87.32 ± 1.34% for valdecoxib respectively at the end of 12 hours. The drug release rate from HPMC K100M matrix was found to be less as compared to ethyl cellulose. This might be due to slow hydration of matrix and its property to form a thick gel layer, it's due to slow erosion of matrix and its property which retard the drug release from the tablet for long duration **(Table 4, Figure 3)**.

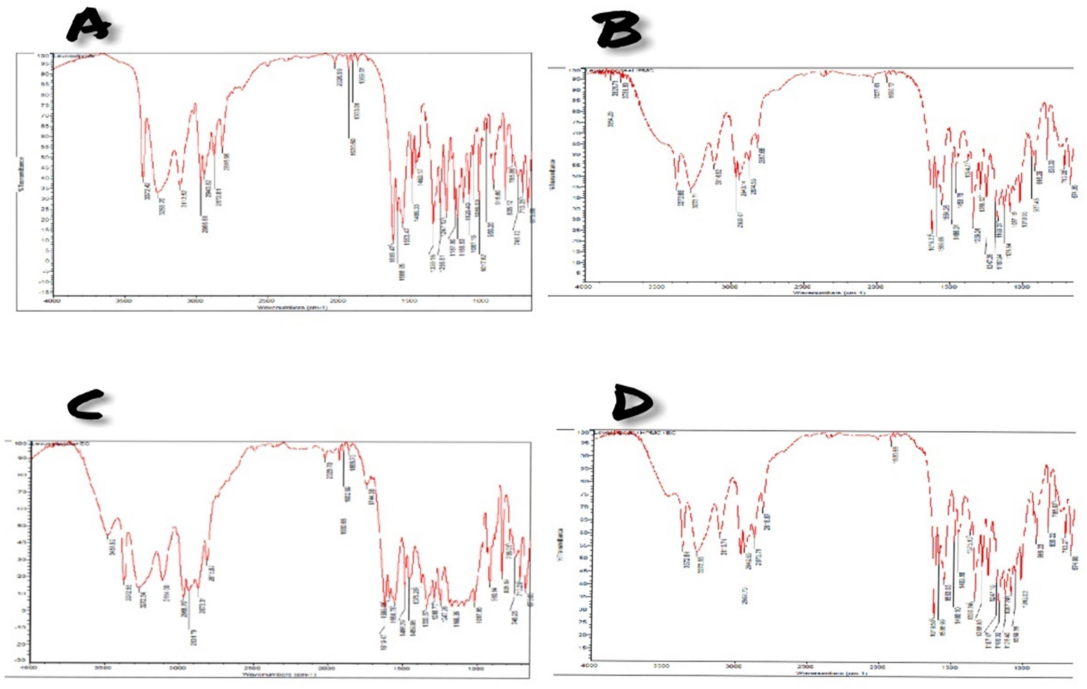

Figure 1: FT-IR spectrum of valdecoxib pure drug(A), solid admixture of valdecoxib +HPMC K100M(B), valdecoxib +ethyl cellulose(C), valdecoxib +HPMC K100 +Ethyl cellulose(D)

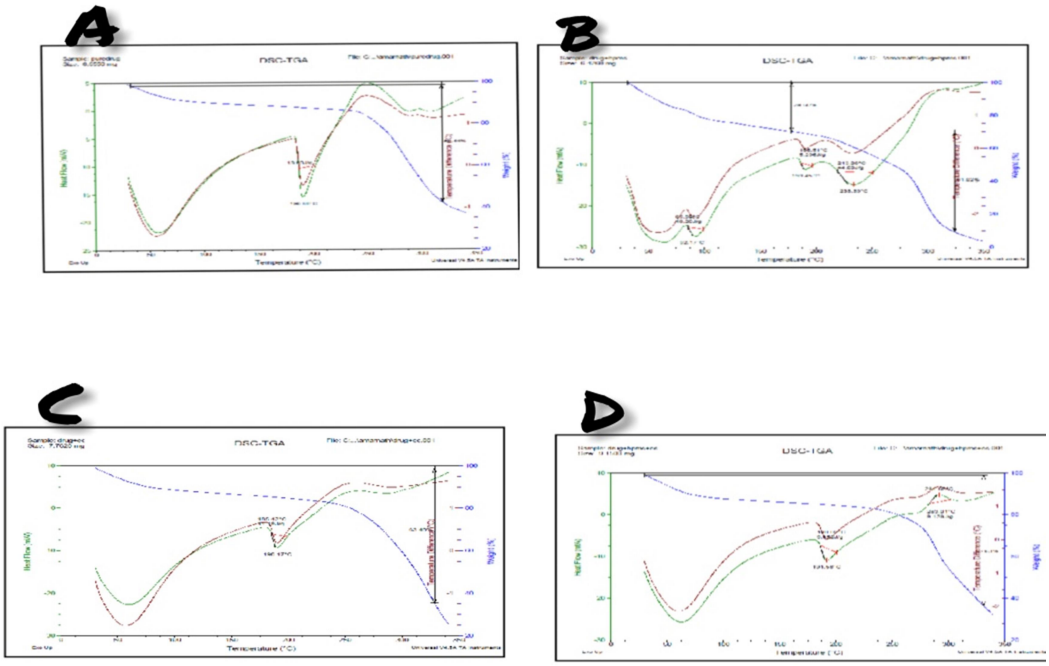

Figure 2: DSC thermograms of valdecoxib pure drug(A), solid admixture of valdecoxib +HPMC K100M(B), valdecoxib +ethyl cellulose(C), valdecoxib +HPMC K100 +Ethyl cellulose(D)

Table 2: Characteristics of powder blend

Formulation Code	Angle of repose (^{0})*	Loose bulk density (g/ml)*	Tapped bulk density (g/ml)*	Hausner ratio*	Carr's index (%)*
VC1	20.64±0.51	0.601±0.00	0.680±0.00	1.13±0.00	11.657±0.57
VC2	19.33±0.49	0.602±0.00	0.669±0.00	1.11±0.01	10.125±1.20
VC3	20.57±0.44	0.595±0.00	0.673±0.00	1.13±0.00	11.660±0.57
VC4	19.51±0.56	0.586±0.00	0.668±0.00	1.14±0.00	12.326±0.57
VC5	20.80±0.31	0.591±0.00	0.677±0.01	1.14±0.01	12.661±1.52
VC6	20.31±0.35	0.579±0.00	0.661±0.00	1.14±0.00	12.326±0.57
VC7	20.08±0.57	0.597±0.00	0.673±0.00	1.12±0.00	11.328±0.57
VC8	19.84±0.21	0.600±0.00	0.670±0.00	1.11±0.00	10.324±0.58
VC9	19.61±0.48	0.582±0.00	0.664±0.00	1.14±0.00	12.330±0.57

***All the values were expressed as mean± SD, n=3**

Table 3: Physical properties of SR matrix valdecoxib tablets

F. Code	Dimension		Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%w/w)
	Diameter (mm)	Thickness (mm)				
VC1	7.76±0.05	3.76±0.05	7.22±0.09	0.298	198.60±2.72	99.71±0.20
VC2	7.93±0.05	3.93±0.05	7.55±0.01	0.297	199.7±2.10	100.35±0.17
VC3	7.63±0.05	3.76±0.05	7.78±0.06	0.249	199.30±2.17	99.12±0.35
VC4	7.73±0.05	3.83±0.05	7.13±0.06	0.284	200.70±2.75	100.76±0.26
VC5	7.86±0.05	3.83±0.05	7.35±0.05	0.394	199.70±2.22	98.82±0.44
VC6	7.83±0.05	3.86±0.05	7.58±0.07	0.397	199.85±2.51	101.29±0.26
VC7	8.06±0.11	4.03±0.05	8.03±0.08	0.488	199.80±1.82	100.59±0.44
VC8	8.03±0.05	4.00±0.10	8.39±0.09	0.348	199.30±2.53	99.06±0.44
VC9	7.86±0.05	3.86±0.05	7.86±0.05	0.348	199.85±1.84	101.64±0.26

***All the values were expressed as mean± SD, n=3**

Table 4: Dissolution profile of formulations VC1 to VC9

Time (Hrs)	Cumulative Percentage Drug Release								
	VC1	VC2	VC3	VC4	VC5	VC6	VC7	VC8	VC9
0	0	0	0	0	0	0	0	0	0
1	7.60±0.76	4.96±1.52	4.52±0.76	8.04±1.32	7.60±0.76	3.64±0.76	4.96±0.76	3.20±0.76	4.96±0.76
2	14.69±1.32	11.59±0.76	10.71±1.32	17.77±0.76	19.53±2.01	9.82±0.76	10.71±1.32	8.06±1.32	13.35±1.32
3	18.73±1.32	19.13±0.75	20.45±0.76	26.67±1.32	30.63±1.33	18.68±1.32	21.33±1.32	14.27±2.02	18.70±1.32
4	27.63±2.03	25.84±0.75	29.36±1.31	36.05±1.33	43.56±2.03	31.10±0.76	30.25±0.76	18.74±1.33	25.85±2.01
5	43.60±3.35	36.54±0.76	37.00±0.75	46.37±1.54	54.36±2.04	45.35±1.33	50.22±0.77	27.65±2.04	35.23±0.76
6	57.08±2.05	48.63±0.76	46.89±1.30	55.43±0.79	60.38±1.36	53.52±1.32	57.53±1.30	33.52±2.66	44.67±0.76
7	67.95±2.06	59.45±0.77	60.35±1.32	63.21±1.35	70.39±0.80	63.50±0.78	64.45±0.01	43.83±2.06	53.71±1.32
8	74.93±2.07	70.34±0.77	71.24±1.31	71.48±1.36	78.70±0.80	70.01±1.33	70.96±0.77	53.31±2.07	63.25±1.33
9	81.93±0.73	78.64±0.77	78.67±0.76	81.11±1.35	84.41±0.81	80.07±0.73	77.51±0.77	60.64±2.70	71.51±1.34
10	85.90±0.81	82.59±1.34	83.50±0.77	87.27±0.81	86.92±2.92	85.79±0.74	82.77±0.02	68.89±2.71	80.26±0.79
11	90.77±0.83	87.44±1.54	87.03±1.33	92.58±1.32	95.03±0.80	89.77±1.34	88.06±0.74	74.98±2.10	85.54±1.33
12	93.90±0.83	90.55±1.55	90.14±1.33	95.28±2.07	97.30±0.06	92.02±0.79	90.29±1.31	80.23±1.42	87.32±1.34

***All the values were expressed as mean± SD, n=3**

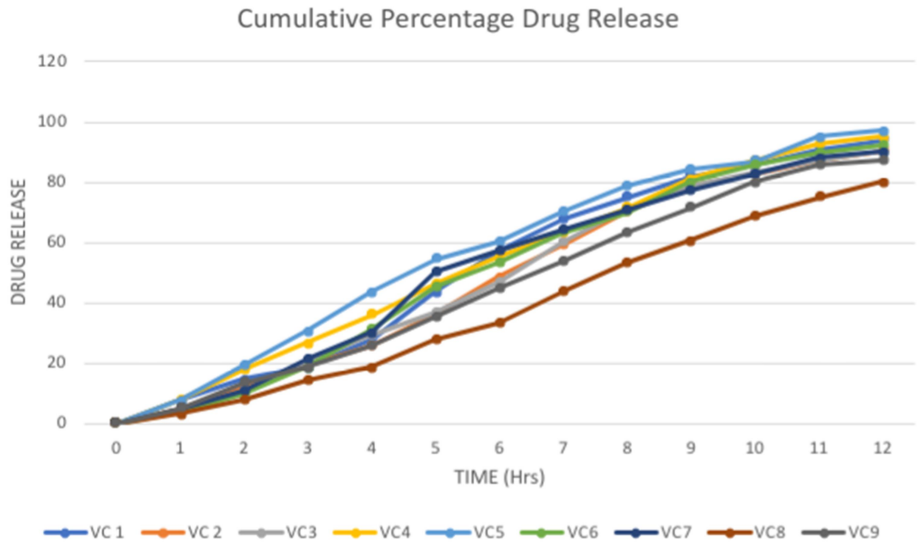

Figure 3: *in vitro* drug release profile of VC1 to VC9

CONCULSION

The sustained release matrix tablets were prepared by the wet granulation method using different polymers like hydroxypropyl methylcellulose, and ethylcellulose as release retardant polymers. The granules were evaluated for angle of repose, bulk density, compressibility index and hausner's ratio. All the tests revealed that granules showed excellent flow properties. The resulting monolithic tablets were evaluated for thickness, diameter, weight variation test, hardness, friability and drug content. All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial standards

In the present studies, matrix formulation VC8 containing HPMC K100M and ethyl cellulose were probably showing maximum retardation of drug release and it shows super case-II transport, for these reasons, it was considered that the formulation VC8 as best formulation among all the nine formulations. From the stability studies, there was no significance difference in hardness, friability, drug content and in vitro release profile for the best formulation.

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