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FORMULATION AND EVALUATION OF NIMESULIDE FLOATING TABLETS BY USING HYDROXY PROPYL METHYL CELLULOSE

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ABSTRACT

In this study, we design and evaluated floating matrix tablets of Nimesulide, to prolong gastric residence time and increase drug absorption to increasing the bioavailability. A simple visible Spectrophotometric method has been employed for the estimation of Nimesulide. Pre-formulation studies were carried out to optimize the required quantity for HPMC (K4M). Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. The tablets were prepared by direct compression technique, using polymer such as hydroxy propyl methyl cellulose (HPMC K4M), in different combinations with other standard excipients like sodium bicarbonate, lactose and Magnesium stearate used as gas generating agent, as filler and as lubricant respectively. Tablets were evaluated for physical characterization viz. hardness, friability, swelling index, floating capacity, thickness and weight variation. Further tablets were evaluated *in-vitro* drug release for 12 hr. The effect of polymer concentrations on buoyancy and drug release pattern was also studied. All the matrix tablets showed significantly greater swelling index and exhibited controlled and prolonged drug release profiles and some floated over the dissolution medium for more than12 hr. The paddle speed affected the floating lag time and floating duration it had a negative effect on the floating properties. It also showed no significant change in physical appearance, drug content, floatability or *in-vitro* dissolution pattern after storage at 45^{o}C at 75 % RH for three months.

KEY WORDS: Nimesulide, Swelling index, Floating capacity, Hydroxy propyl methyl cellulose (HPMC)

1. INTRODUCTION

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is be filled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility. Furthermore, the relatively short gastric emptying time in humans this normally averages 2-3 hrs. Through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. After oral administration, such a dosage forms would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. Gastro-retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients.

2. MATERIALS AND METHODS

Nimesulide was obtained as a gift sample from Micro Lab Ltd. Hydroxy propyl methyl cellulose was obtained from Fine chem Ltd, Sodium Bicarbonate was obtained from Micro Labs Ltd, Lactose, Citric acid, Aerosol was obtained from Arvind chem Ltd, Chennai.

2.1. Preparation of floating matrix tablet of Nimesulide: Tablets were fabricated by using wet granulation technique. Nimesulide was mixed with required amount of polymers and other excipients. All the excipients were passed through # 60 mesh, mixed and granulated with 10% solution of PVP K 90 in isopropyl alcohol. The wet mass was passed through #16 mesh and dried at 45oC for 2 hrs. Dried granules were passed through #24 mesh and mixed with magnesium stearate and talc. Granules were compressed into tablets using 16 punch single station tablet compression machine (Cadmach).

2.2. Evaluation parameters of Nimesulide tablets: Nimesulide floating tablets were evaluated for physical parameters like hardness, friability test, weight variation tests and they were also evaluated for floating parameters like buoyancy lag time, swelling index and dissolution studies.

2.3 *In-vitro* Dissolution study: Dissolution of the tablet of each batch was carried out using USP type II apparatus using paddle. 900 ml of 0.1N HCL (pH 1.2) was place in a dissolution vessel and the temperature of the medium was set at 37± 0.5^{o}C. One tablet was placed in each dissolution vessel and the rotational speed of paddle was set at 100rpm. The 10ml of sample was withdrawn at predetermined time intervals for 10 hours and was replaced with same volume of fresh dissolution medium. The samples were taken at 0.5, 1, 2, 4, 6, 10, 12, and 24hrs. The sample were filtered and diluted to suitable concentrations with 0.1N HCL solution. The absorbance of the solution was measured at 393nm for Nimesulide with UV spectrophotometer.

3. RESULTS

The FTIR spectrum of pure drug and physical mixture of drug and polymer were studied using FTIR spectrophotometer. The peaks obtained in the spectra's of each formulation correlated with the peaks of drug spectrum. From the FTIR spectrum, it was concluded that no significant difference in peak pattern in IR spectrum of drug, polymer, excipients. The values obtained for angle of repose for F1-F6 are tabulated in Table.2. The values indicates good flow property of the powder blend. As the concentration of HPMC K_4M, HPMC $K_{15}M$, HPMC $K_{100}M$ increases, the angle of repose and Carr's index increase while the flow rate decrease. Compressibility index ranges between 12.5% and 17.5% indicating that the powder blend has the required flow property for wet granulation method as shown in Table.No:2. The entire tablet passed weight variation test as the percentage weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values as shown in Table.3. The measured hardness of tablet of each batch range between 3.2 to 4.4 kg/cm^2 as shown in Table.3. The percentage of drug content was found to be 98.76% to 101.36% of, which Nimesulide was within acceptable limits. The friability values was found to be less than 1% in all cases and considered to be satisfactory. In the present study, the higher swelling index was found for tablets of F6 containing 30% HPMC$K_{100}M$. Thus, the concentration of polymer and ratio of lactose had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and concentration ratio as shown in Table.6 From the *in-vitro* drug profiles, it was found that drug release rate increased as the concentration of HPMCK_4 M increased. It was also concluded that the drug release rate was decreased by HPMC K_4M, HPMC $K_{15}M$, as that of lactose. The rate of drug release increased as tabulated in Table.11 and Figure.8

Table no 1: **Formula Table of Nimesulide floating tablets**

S.NO	Ingredients	Quantity for one tablet					
		F1	F2	F3	F4	F5	F6
1	Nimesulide	100mg	100mg	100mg	100mg	100mg	100mg
2	HPMC K_4M 25%	75mg	-	-	-	-	-
3	HPMC K_4M 30%	-	90mg	-	-	-	-
4	HPMC $K_{15}M$ 25%	-	-	75mg	-	-	-
5	HPMC $K_{15}M$ 30%	-	-	-	90mg	-	-
6	HPMC $K_{100}M$ 25%	-	-	-	-	75mg	-
7	HPMC $K_{100}M$ 30%	-	-	-	-	-	90mg
8	Lactose	84mg	69mg	84mg	69mg	84mg	69mg
9	Citric Acid	5mg	5mg	5mg	5mg	5mg	5mg
10	Sodium Bi Carbonate	30mg	30mg	30mg	30mg	30mg	30mg
11	PVP K90	1.5mg	1.5mg	1.5mg	1.5mg	1.5mg	1.5mg
12	Iso Propyl Alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
13	Talc	1.5mg	1.5mg	1.5mg	1.5mg	1.5mg	1.5mg
14	Aerosil	1mg	1mg	1mg	1mg	1mg	1mg
15	Magnesium Stereate	2mg	2mg	2mg	2mg	2mg	2mg

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Table no 2 Evaluation of different parameters of Nimesulide Floating Tablets

Batch Code	Bulk Density (g/cc)	Tappped Density (g/cc)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose	Floating Lag Time (sec)	Total Floating Time (hrs)
F1	0.469	0.536	12.5	1.14	25º31'	5.0	>12
F2	0.474	0.552	14.1	1.16	26º3'	6.0	>12
F3	0.476	0.564	15.6	1.18	27º10'	5.0	>12
F4	0.478	0.573	16.5	1.19	28º47'	7.0	>12
F5	0.484	0.586	17.4	1.21	28º36'	5.0	>12
F6	0.488	0.592	17.5	1.21	29º23'	6.0	>12

Table No 3 Evaluation Parameters of Nimesulide Floating Tablets

Batch Code	Evaluation Parameters						
	Average Weight of Tablets (mg)	Hardness (kg/cm²)	Percentage Friability (%)	Drug Content (%w/w)	General Appearance	Thickness (mm)	Diameter (mm)
F1	302	3.2	0.546	98.76	Oval	5.04	10.12
F2	301	3.4	0.578	99.72	Oval	5.03	10.15
F3	298	3.5	0.652	99.32	Oval	5.06	10.08
F4	296	4.2	0.582	100.34	Oval	5.10	10.11
F5	302	4.2	0.416	101.36	Oval	5.12	10.12
F6	306	4.4	0.432	98.96	Oval	5.08	10.13

Table no 4 Degree of Swelling of Nimesulide Floating Tablets

Time (hrs)	Degree of Swelling (%)					
	F1	F2	F3	F4	F5	F6
1	76	88	90	94	96	104
2	84	97	98	108	114	136
3	86	112	114	124	132	158
4	108	120	127	154	148	178
5	114	137	148	168	176	186
6	132	148	179	208	196	214
7	154	167	188	226	218	258
8	168	186	202	242	264	276

Table No 5 *In-vitro* Dissolution Profile of Nimesulide Floating Tablets

Time (hrs)	Percentage Cumulative Drug Release					
	F1	F2	F3	F4	F5	F6
0.5	10.83	10.51	10.42	10.21	9.91	9.64
1	19.40	19.10	18.80	18.21	18.20	17.91
2	34.66	34.32	34.04	34.03	32.69	31.91
4	49.63	48.87	48.16	47.23	46.75	46.33
6	60.51	59.60	59.31	58.07	58.68	57.78
10	81.71	80.20	83.25	79.29	78.98	78.68
12	92.75	90.31	90.03	90.00	89.38	87.02
24	100.42	100.31	100.14	99.96	98.60	98.36

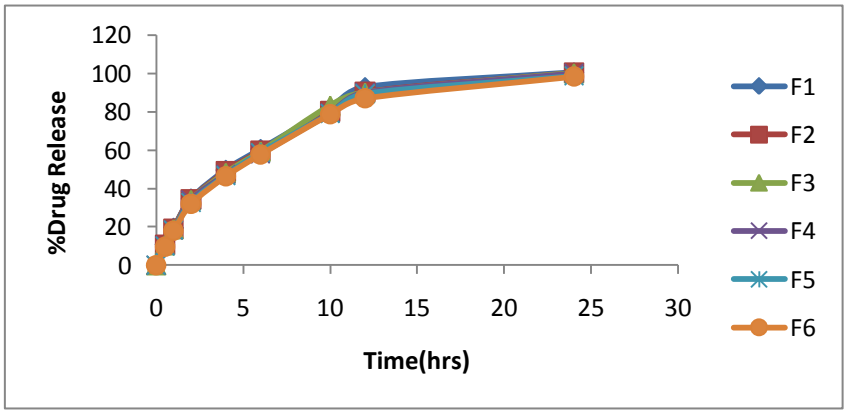

Figure No 1 *In-vitro* Dissolution Profile of Nimesulide Floating

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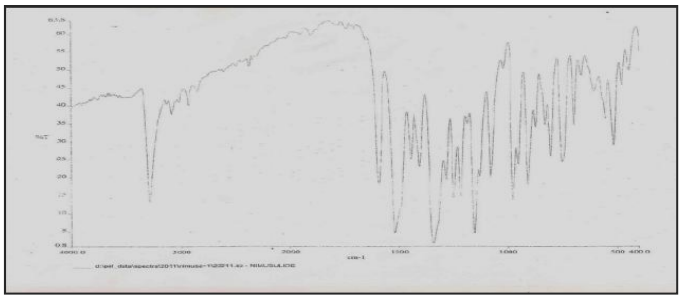

Figure No 2 IR spectrum of pure drug, Nimesulide

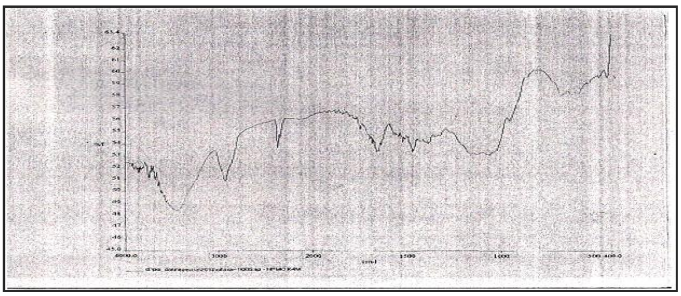

Figure No 3 IR spectrum of HPMC $k_{15}M$

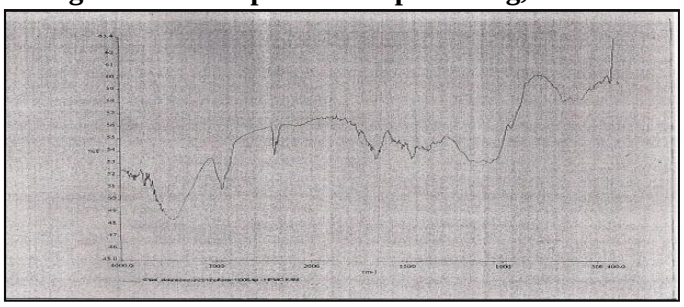

Figure no 4 IR spectra of HPMC $k_{100}M$

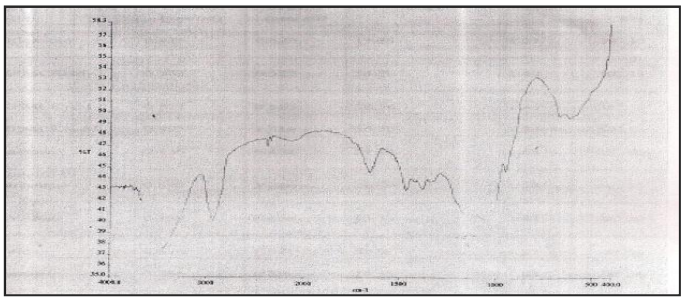

Figure no 5 IR spectrum of Nimesulide and HPMC k_4M

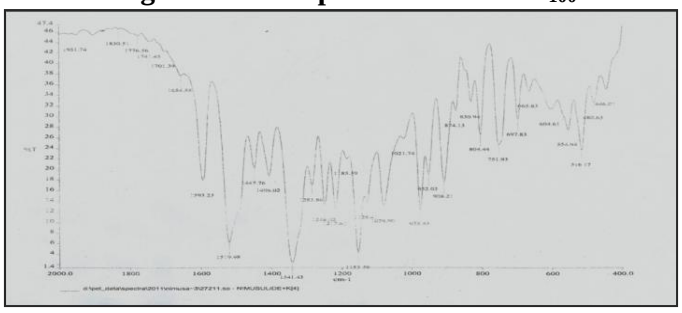

Figure no 6 IR spectrum of nimesulide and hpmc $k_{15}M$

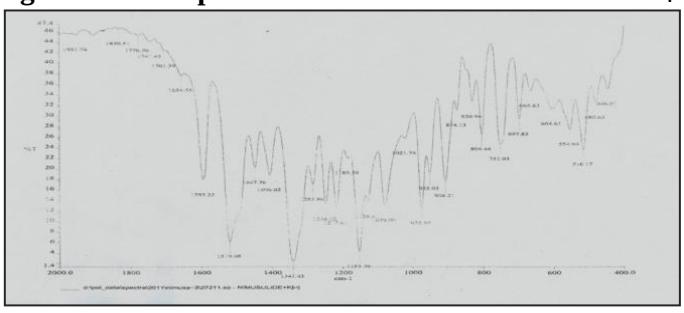

Figure no 7 IR spectrum of Nimesulide and HPMC $k_{100}M$

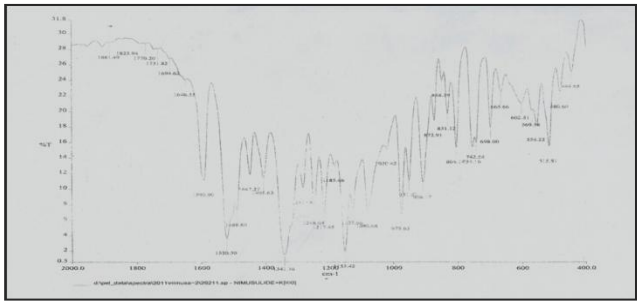

Figure no 8 IR spectrum of Nimesulide and HPMC $k_{100}M$

4. CONCLUSION

The floating tablets were prepared using different polymer grades like HPMC K_4M, HPMC $K_{15}M$ & HPMC $K_{100}M$ polymers. The grades of HPMC increased the viscosity by increasing the time of drug release (decrease the drug release). Tablets are subjected to various evaluation parameters such as physical property, floating property, swelling property & in - vitro drug release studies. It was revealed that all batches had acceptable physical parameters. All tablet formulation adds good floating property along with swelling behaviors & in – vitro drug release.

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