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Prodrugs of Ibuprofen I: Preparation and Physico-chemical Properties

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The hydrochloride salts of N-Mannich bases of ibuprofenamide, which in turn was prepared using either morpholine or piperidine as the amine component. The characterization of the N-Mannich bases was done by element analysis, IR spectroscopy and NMR spectroscopy. Physico-chemical properties such as solubility, dissolution-rate and partition-coefficient were determined. The hydrochloride salt of N-Mannich bases of ibuprofenamide prepared using morpholine was found to be water soluble whereas the one prepared using piperidine was found to be water insoluble. The dissolution rate studies showed that dissolution rate of N-Mannich base of ibuprofenamide was pH-independent whereas that of piperidine was pH-dependent.

The gastrointestinal ulcerogenicity poses major drawback in the use of non-steroidal antiinflammatory drugs (NSAID) for long term therapy of arthritis and other rheumatic diseases. There is always a need for safer NSAIDs and research efforts are on going for developing safer NSAIDs. The prodrug approach is one of the most promising ones in these approaches. The most common approach for preparing a prodrug is to change the drug containing -COOH or -OH group to esters; so the prodrug of antiinflammatory agents liberate the active species upon metabolism. Many ester derivatives of ibuprofen have been prepared and found effective[1-3].

N-Mannich bases have been proposed to be potentially useful prodrug candidates for NH-acidic compounds; such as various amides, imides, carbamates, hydantoins and urea derivatives as well as for aliphatic or aromatic amines[4]. N-Mannich base of ibuprofen can be prepared as a prodrug first by converting -COOH group of ibuprofen to $-CONH_2$ and then converting the amide into the N-Mannich bases. N-Mannich bases in aqueous solution get decomposed by hydrolysis and the rate is highly dependent upon the pH of the medium and structu e of the substrate[5-13].

The physico-chemical properties of a drug play a major role in the total bioavailability and its pharmacokinetic pattern. In the present work, the solubility, partition-coefficient and the dissolution rate of the synthesized N-mannich bases of ibuprofenamide were investigated.

MATERIALS AND METHODS

Two prodrugs of ibuprofen were synthesized as N-Mannich bases of ibuprofenamide. These are N-(morpholinomethyl) ibuprofenamide hydrochloride (IBMB-M) and N-(piperidinomethyl) ibuprofenamide hydrochloride (IBMB-P).

Preparation of ibuprofenamide:

Ibuprofen (2.06 g., 0.01 mol) and thionyl chloride (10 ml) were refluxed for 2 h until the evolution of hydrogen chloride and sulphur dioxide almost ceased. The excess of thionyl chloride was distilled out when the acid chloride of ibuprofen was obtained as a thick liquid. The acid chloride was added dropwise to a well-stirred ice cooled liquor ammonia solution (50 ml). The amide of ibuprofen was filtered and crystallized from water-ethanol mixture (40:60 v/v). Elemental analy-

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sis: calcd. for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.8; H, 9.20; N, 6.95. IR (KBr): 850 cm^{-1} (para-di-substitution), 1380, 1390 (gem-di-methyl substitution), 1660 (-CO-), 2860-2960 (aromatic –CH-), 3200, 3380 (-$CONH_2$). ^1H NMR: 0.87 (6H, d, J=6 Hz, CH ($C\underline{H}_3$)$_2$, 1.5 (3H, d, J=7 Hz; $CHC\underline{H}_3$), 1.9 (1H, M, $C\underline{H}$ (CH_3)$_2$), 2.45 (2H, d, J=6 Hz, CH2-Ar), 3.55 (1H, q, J=6 Hz, CH-CH_3), 7.12 (4H, 1S, ArH).

Preparation of IBMB-M:

A mixture of ibuprofenamide (2.05 g, 0.01 mol), paraformaldehyde (0.45 g, 0.015 mol) and morpholine (1.3 ml, 0.015 mol) was refluxed in ethanol (20 ml) for 9 h. The solvent was removed under vacuum when the crude product was obtained in the form of reddish oil. The product was washed thrice with distilled water and dried at room temperature in a desiccator. It was dissolved in ethanol (20 ml) and the solution cooled in ice-bath. Dry hydrogen chloride was passed through the solution; when the hydrochloride of N-mannich base separated out. The product was crystallized from ethanol. Elemental analysis: calcd. for $C_{18}H_{29}N_2O_2Cl$: C, 63.42; H, 8.58; N, 8.21; Cl, 10.4. Found: C, 63.71; H, 8.48; N, 8.10; Cl, 10.23. IR (KBr): 860 cm^{-1} (para-di-substitution), 1380, 1390 (gem dimethyl substitution), 1695 (-CO-), 2500-2750 (aliphatic -CH-), 2880-3050 (aromatic -CH-). ^1H NMR: 0.85 (6H, d, J=6Hz, CH($C\underline{H}_3$)$_2$), 1.52 (3H, d, J=7Hz, CH-$C\underline{H}_3$), 2.45(1H, m, $C\underline{H}$(CH_3)$_2$, 2.48 (2H, d, J=6 Hz, CH_2-Ar), 3.05 (7H, m, $C\underline{H}$-CH_3, $C\underline{H}_2$-N(CH_2-)$_2$), 3.95 (4H, m, O($C\underline{H}_2$-)$_2$, 7.15 (4H, s, ArH).)

Preparation of IBMB-P:

Using ibuprofenamide (2.05 g, 0.01 mol), paraformaldehyde (0.45 g, 0.015 mol) and piperidine (1.5 ml, 0.015 mol) and following the above procedure IBMB-P was obtained.

Elemental analysis: calcd. for $C_{19}H_{31}N_2O_2Cl$: C, 67.34; H, 9.22; N, 8.26; Cl, 10.6. Found: C, 67.3; H, 9.0, N, 8.31; Cl, 10.8. IR (KBr): 840 CM^{-1} (para-di-substitution), 1370, 1380 (gem-dimethyl substitution), 1695 (-CO-), 2560-2640 (aliphatic -CH-), 2850-2980 (aromatic -CH-). ^1H NMR: 0.9 (6H,d, J=6Hz, CH ($C\underline{H}_3$) $_2$), 1.5 (3H,d, J=7 Hz, CH-$C\underline{H}_3$), 1.5 (6H, m, -$C\underline{H}_2$-$C\underline{H}_2$-$C\underline{H}_2$ of piperidine), 2.4 (9H, m, $C\underline{H}$(CH_3) $_2$, CH_2-N ($C\underline{H}_2$-)$_2$, $C\underline{H}_2$-Ar), 3.5 (1H, m, J=7 Hz, $C\underline{H}CH_3$), 7.1 (4H, m, ArH).The analytical data and yields are given in Table 1.

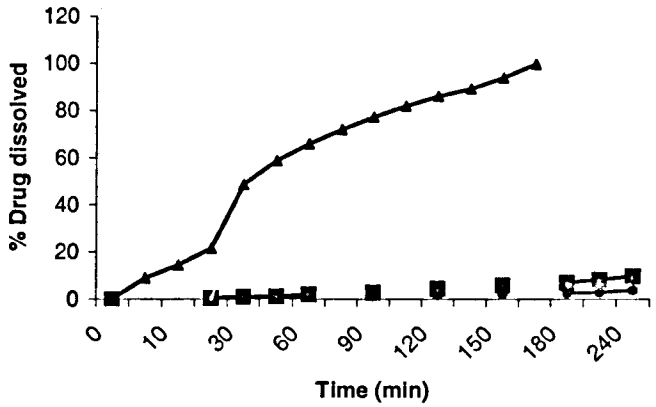

Fig. 1: Dissolution rate profile of ibuprofen.

Dissolution rate studies of ibuprofen were performed at different pH at 37° at pH 1.2 (-●-), pH 4.7 (-■-) and pH 7.4 (-▲-).

Solubility in water:

The solubilities of IBMB-M and IBMB-P were determined in triplicate by stirring an excess of IBMB-M/IBMB-P in water (5 ml) with a magnetic stirrer for 4 h at 25° and 37° in a sealed flask. The supernatant was filtered through a nylon filter and the portion of the filtrate was suitably diluted with water. The concentration of IBMB-M and IBMB-P were determined by measuring the UV absorbance at 220 nm.

Solubility in alcohol and chloroform:

The solubilities were determined in triplicate by using an excess of drug in ethanol at 25°. The procedure was same

TABLE 1: STRUCTURE, ANALYTICAL DATA AND YIELD OF SYNTHESISED PRODRUGS.

General Formula: CH_3-CH (CH_3)-CH_2-C_6H_6-CH (CH_3)-CONHR

Compound	R	Molecular Formula	Molecular Weight	Yield (%)	Melting Point (°)
IBA	H	$C_{13}H_{19}NO$	205	80	115-116
IBMB-M	C_4H_8NO	$C_{18}H_{29}N_2O_2Cl$	340.5	60	195-198
IBMB-P	$C_5H_{10}N$	$C_{19}H_{31}N_2OCl$	338.5	58	180-182

IBA = Ibuprofenamide, IBMB-M = N-(morpholinomethyl) ibuprofenamide hydrochloride, IBMB-P = N-(piperidinomethyl) ibuprofenamide hydrochloride.

TABLE 2: SOLUBILITY AND PARTITION-COEFFICIENT OF THE SYNTHESIZED PRODRUGS.

Solvent/ Temp.	Solubility as mg/ml		System	Partition -Coefficient	
	IBMB-M	IBMB-P		IBMB-M	IBMB-P
Water-25°	61	13	Chloroform-Water (1:1) at 25°	2.59	4.14
Water-37°	226	14.2	Octanol-pH 1.2 buffer (1:1) at 37°	5.9	18.61
Alcohol-25°	30	50			
Chloroform –25°	98	160			

IBMB-M = N-(morpholinomethyl) ibuprofenamide hydrochloride, IBMB-P = N-(piperidinomethyl) ibuprofenamide hydrochloride.

as adopted for water solubilities except the dilution of the filtrate were made in ethanol only. For determine solubility in chloroform an excess amount of the drug was stirred in chloroform at 25° for 4 h in a sealed flask. The supernatant was filtered through nylon filter and 3 ml of the filtrate was taken in the previously weighed china dish. The solvent was evaporated off and the weight of the residue determined. The solubility was calculated as mg/ml. Results are shown in Table 2.

Determination of partition-coefficient:

The partition-coefficient of IBMB-M and IBMB-P were determined in two systems: (a) chloroform-water system (b) octanol-pH 1.2 buffer system. One hundred milligrams of IBMB-M/IBMB-P was added to 10 ml of aqueous phase, and then 10 ml of organic phase was added to it. The mixture was shaken for 30 sec at 10 min interval for 1 h period and left for 2 h at 25°. Two layers were separated out using separating funnel. Concentration of the drug in aqueous phase was determined by measuring the UV absorption at 220 nm. The partition coefficient was calculated as concentration of drug in organic phase/concentration of drug in aqueous phase. Results are shown in Table 2.

Dissolution rate studies:

In vitro dissolution rate studies of IBMB-M, IBMB-P and ibuprofen were carried out in the Electrolab Dissolution Tester 6 station USP Discs (pellets) of the drug of 100 mg and 11.3 mm diameter were prepared using Hydraulic press; by compressing at 4000 kg/cm² pressure for one minute. The discs were placed in the wire basket and suspended in the vessel containing 500 ml of dissolution medium, maintained at 37°.

The dissolution media were, hydrochloride buffer (pH 1.2), acetate buffer (pH 4.7) and phosphate buffer (pH 7.4). The baskets were rotated at 100 RPM. Five millilitres of the sample was withdrawn at each time interval and replaced with equal volume of fresh dissolution medium. The samples were suitably diluted and absorbance measured at λ_{max} of the drug in that buffer. The release profiles were plotted as percent drug dissolved vs. time and depicted in fig.1-3.The values of correlation coefficient (r), dissolution rate (k) and time to dissolve 50% drug ($t_{50\%}$) are given in Table 3.

RESULTS AND DISCUSSION

The N-Mannich bases of amide of ibuprofen were prepared using two different bases (amine) as, IBMB-M using morpholine as a base and IBMB-P using piperidine as a base. The hydrochloride salts of these N-Mannich bases were obtained in the form of crystals.

The characterization of the synthesized prodrugs was done by elemental analysis, Infra-red spectroscopy and NMR spectroscopy. Elemental analysis of all the products was found within permissible limits. Infra-red spectroscopy confirmed the structure by showing the characteristic absorption bands of these compounds. Also in NMR spectroscopy

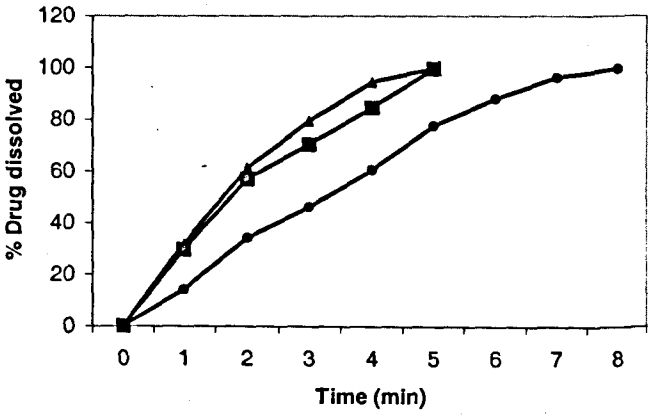

Fig. 2: Dissolution rate profile of IBMB-M.

Dissolution rate studies of IBMB-M were performed at different pH at 37° at pH 1.2 (-●-), pH 4.7 (-■-) and pH 7.4 (-▲-).

TABLE 3: DISSOLUTION RATE STUDIES OF IBUPROFEN, IBMB-M AND IBMB-P.

Sr. No.	Drug	pH	r	K (%/min)	$t_{50\%}$ (min)
1	Ibuprofen	1.2	0.9947	0.0155	-
		4.7	0.9975	0.0377	-
		7.4	0.9429	-	-
2	IBMB-M	1.2	0.9857	14.5	3.5
		4.7	0.9885	22.5	2.2
		7.4	0.9682	26	1.9
3	IBMB-P	1.2	0.9894	0.53	90.2
		4.7	0.9899	8	6.1
		7.4	0.7853	-	-

IBMB-M= N-(morpholinomethyl) ibuprofenamide hydrochloride, IBMB-P = N-(piperidinomethyl) ibuprofenamide hydrochloride

all the compounds gave signals at expected values as governed by their chemical structure.

The solubilities of IBMB-M and IBMB-P were determined in water, alcohol and chloroform. IBMB-M was found to be more soluble in water as compared to the IBMB-P. At 25°, the solubility of IBMB-M was found to be 61 mg/ml as compared to 13 mg/ml of IBMB-P. There was manifold increase in the solubility of IBMB-M in water at 37°, i.e., 61 mg/ml at 25° to 226 mg/ml at 37°. But there was no effect of temperature on the solubility of IBMB-P. IBMB-P was found to be more soluble in alcohol and chloroform as compared to IBMB-M.

A measurement of drug's lipophilicity and an indication of its ability to cross cell membrane is oil/water partition-coefficients in system such as octanol/water and chloroform/water. The partition-coefficients of IBMB-M and IBMB-P were determined in two systems. The partition-coefficient of IBMB-M in chloroform-water system (at 25°) was found to be 2.59 and in octanol-pH 1.2 buffer system (at 37°) was 5.90. But there was remarkably high partition-coefficient of IBMB-P in chloroform-water system, 4.14 and in octanol-pH 1.2 buffer system, 18.61.

From the solubility and partition-coefficient data we can conclude that IBMB-M is hydrophilic and IBMB-P is lipophilic in nature. The only difference of bases used in synthesis of N-Mannich bases of ibuprofenamide has brought about such a drastic difference in the nature of two compounds. This can be rationalized on the structure of the two N-Mannich

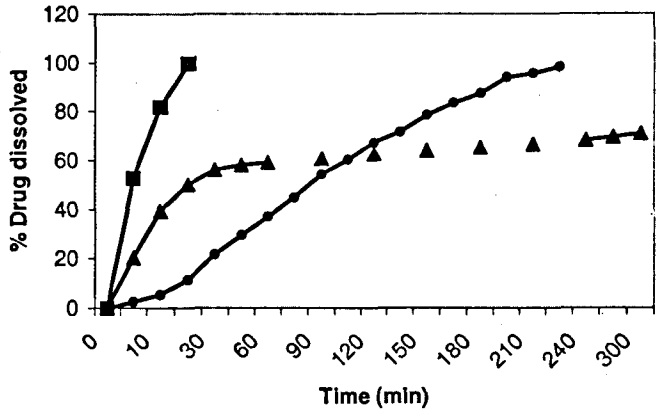

Fig. 3: Dissolution rate profile of IBMB-P.

Dissolution rate studies of IBMB-P were performed at different pH at 37° at pH 1.2 (-●-), pH 4.7 (-■-) and pH 7.4 (-▲-).

bases, the morpholine ring has an additional oxygen atom, which can form hydrogen bonds with water and increase its solubility in water. On the other hand, in IBMB-P, the piperidine ring is much more hydrophilic than morpholine as besides the nitrogen atom the remaining ring has only hydrophobic methylene groups. The total solubility of acids or bases in aqueous medium is dependent on the pH. For this reason the dissolution rate studies were performed at different pH values such as, pH 1.2, pH 4.7 and pH 7.4, which represented the pH of stomach, duodenum and jejunum, respectively.

IBMB-M showed very good dissolution rate pattern. There was not much effect of pH on the dissolution of compound and 100% of the drug was dissolved within 7 min at all the three pH. The graph of % drug dissolved vs. time was found to be linear from which we can conclude that dissolution rate was following zero-order kinetics. The $t_{50\%}$ values were 3.5, 2.2 and 1.9 min at pH 1.2, 4.7 and 7.4, respectively. On the other hand, the dissolution rate pattern was totally different for IBMB-P. The solubility and dissolution rate was found to be very much pH-dependent. At pH 7.4, 100% drug was dissolved within 15 min, while at pH 1.2, it took about 225 min to dissolve 100% drug. The dissolution followed zero-order kinetics. But at pH 7.4 approximately 60% drug was dissolved in 45 min but after that the release was almost constant. Hence, the dissolution rate was found not to follow zero-order kinetics.

The dissolution rate of ibuprofen was also found to be pH-dependent. As the solubility of ibuprofen in acid medium is very less, the dissolution rate of ibuprofen at pH 1.2 and

pH 4.7 was very slow. In 4 h, only 4% of the drug was dissolved at pH 1.2 and 10% of the drug was dissolved at pH 4.7. Since ibuprofen is soluble in alkaline medium, the dissolution rate of ibuprofen was high at pH 7.4. In the first 45 min, approximately 60% of the drug was dissolved but after that the dissolution was very slow and took 165 min for complete dissolution.

The results of this study show that large modification in the aqueous solubility, dissolution-rate and lipophilicity can be achieved through N-Mannich base formation. It is possible to modify the solubility and the dissolution characteristics selecting the appropriate amine component and salt form. The N-Mannich bases of ibuprofen amide prepared using morpholine as an amine component, was found to have very good aqueous solubility and dissolution characteristics comparable to the parent drug ibuprofen.

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