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EFFECT OF pH ON DISSOLUTION BEHAVIOUR OF COMMERCIALLY AVAILABLE DICLOFENAC SODIUM TABLETS

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Abstract: This study was performed at different pH on six brands of commercially available enteric-coated diclofenac sodium tablets. Dissolution behaviour of all the six brands was studied using USP type-II dissolution apparatus, working at 50 rpm. The data thus collected were plotted on standard curves constructed by using different concentrations of pure diclofenac sodium. Amount of diclofenac sodium dissolved in dissolution medium was obtained and the amount remaining undissolved was calculated. The data were analyzed using cube-root law to calculate the dissolution rate constants. The difference in dissolution behaviour among the brands may be due to the difference in film coating material, although other factors such as size and age of granules, compression force and the use of hydrophobic excepients may also play their part in causing variation in the dissolution behaviour of these brands.

Keywords: Diclofenac Sodium, Dissolution behaviour, Hydrophobic excepients

INTRODUCTION

Diclofenac sodium is a white crystalline powder. It is hygroscopic, soluble in water and insoluble in organic solvents. Diclofenac sodium is a cyclooxygenase inhibitor and possesses analgesic, anti-pyretic and anti-inflammatory actions. It is widely used to relieve painful arthritic conditions. The drug is rapidly and completely absorbed after oral administration. Peak plasma concentration occurs after two hours of administration of enteric-coated tablets, its plasma half-life is 1-2 hours. Enteric-coated dosage forms are those that remain intact in stomach but dissolve and release their contents on arriving in small intestine. Factors responsible for this include the difference in pH of gastric and intestinal fluids; where the coatings that are acid functionally or acid ester functionally remain unionized and remain intact in the low pH (pH 1-4) gastric environment, they ionize and thus disintegrate in the intestinal fluids where the pH may vary from 5 in the duodenum to around 7.4 further down the intestinal tract [Banker and Anderson 1987]. Other factors responsible for loss of film integrity include hydration and the presence of esterase in the intestinal fluid that are responsible for cleavage of ester linkage present in some kinds of enteric films [Lehman 1989]. Dissolution is the process by which a solvent dissolves the drug. In biological systems, drug dissolution in aqueous medium is an important condition for systemic absorption [Shargel and Andrew 1980]. In vitro dissolution tests have been extensively studied, developed and used as a measurement of bioavailability. These tests have proved to be a reliable measure for the estimation of in vivo drug release behaviour. Dissolution of the drug occurs not only from the fine particles that are ultimately

produced but also results, although only to a small extent, from the intact dosage form before its disintegration and from the fragments and agglomerates produced after disintegration. Although dissolution kinetics may be influenced by the physiochemical characteristics of the drug and the formulation factors, however, since the study was carried out different brands of the same drugs, the most probable variants in this case could be the kind of coating materials used, the coating material thickness, the amount of plasticizer used and the age of the coating film.

MATERIALS AND METHODS

Six compressed oral formulations of enteric-coated diclofenac sodium tablets were tested. Each tablet contains 50 mg diclofenac sodium. Tablets of same batches were used throughout the study. Their technical data are given in Table 1. Pure diclofenac sodium used as reference standard was provided by Orta Laboratories Lahore, Pakistan. Analytical grade sodium hydroxide (Merck), potassium dihydrogen phosphate (Merck), and 37% HCl (Merck) were used. Distilled water (pH 6.8 ± 0.2 as

Table 1: Technical Data of Drugs Used

Name of Formulation	Manufacturer	Batch No.	%age weight variation	Hardness in Kgs	Disintegration Time (min)	Assay
D1=Voltral (50 mg)	Novartis	017	0.23	18.5	30	100.50%
D2=Artifen (50 mg)	Abbott	52180 xu	0.56	19.2	35	100.21%
D3=Dicofen (50 mg)	Glaxo-Welcome	0029	0.29	19.2	38	100.91%
D4=Penfen (50 mg)	Atco	90.008	0.34	20.1	40	99.70%
D5=Dyclo (50 mg)	Indus	200	0.28	18.75	35	101.0%
D6=Sonal (50 mg)	Pharma Care	3855	0.31	18.5	35	101.0%

measured at Orion pH meter) obtained from all glass electrically heated still and stored in thoroughly washed, well stoppered 5 litre plastic bottles was used throughout the research. The dissolution test specified in USP XXII for diclofenac sodium tablets was conducted on all the brands. Apparatus used for this purpose was USP dissolution apparatus II (type DT. model D-6072, ERWEKA APPARATEBAU-GmbH). Dissolution medium used was 900 ml of simulated gastric (0.1N HCl adjusted to pH 1.2) and simulated intestinal media (mixed phosphate buffer) at pH 4.0, 4.5, 5.5, 6.0 6.5 and 7.0. Media were maintained at 37±0.5 ^{0}C and rotation speed was set at 50 rpm. 10 ml samples were drawn from the dissolution vessel at specified time intervals and the volume of dissolution test medium was kept constant by adding same volume of fresh dissolution medium after each withdrawal. Samples were analyzed spectrophotometrically, absorbance was noted at 276 nm, and plotted on a standard curve constructed by making standard dilutions of pure

diclofenac sodium ranging from 0.001 gm/100ml to 0.008 gm/100ml and noting their absorbance at 276nm. Absorbance of samples drawn at different time intervals and at different pH was plotted on these standard curves constructed for media of different pH. The percentage of the drug dissolved at a particular time interval was calculated with the help of following relation.

$$Percentage\,dissolved = \frac{x\,mg/100\,ml}{Assay\ amount} \times 100$$

RESULTS AND DISCUSSION

Results of weight variation, hardness test and disintegration test performed on these tablets are given in Table 1. Dissolution test performed at pH 1.2 (simulated gastric fluid) did not give any results for any of the brands for up to two hours thus fulfilling the USP criteria for enteric coating. Results of dissolution tests carried out at different pH are given in Table 2. Although almost all the brands released 100% of their

Table 2(a): Percentage Diclofenac Sodium Dissolved at pH 4 and 4.5

Time	pH 4.0						pH 4.5					
(min)	D1	D2	D3	D4	D5	D6	D1	D2	D3	D4	D5	D6
15	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12.3	0.0
60	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	35.1	0.0
90	0.0	0.0	0.0	0.0	0.0	0.0	11.1	0.0	0.0	0.0	55.6	0.0
120	0.0	0.0	0.0	0.0	0.0	0.0	25.4	20.7	0.0	0.0	65.0	0.0
150	0.0	0.0	0.0	0.0	0.0	0.0	30.6	35.5	0.0	0.0	67.8	0.0
180	0.0	0.0	0.00	0.0	0.0	0.0	45.4	48.5	0.0	0.0	70.2	22.7
210	29.9	30.5	26.7	21.4	28.0	32.8	56.1	60.3	32.3	21.0	79.8	50.8
240	49.0	50.5	52.6	49.9	51.5	54.0	61.0	72.2	72.5	49.4	81.2	65.0

Table 2(b): Percentage Diclofenac Sodium Dissolved at pH 5.5 and 6.0

Time	pH 5.5						pH 6.0					
(min)	D1	D2	D3	D4	D5	D6	D1	D2	D3	D4	D5	D6
15	30.9	0.0	11.4	0.0	0.0	21.8	51.5	0.0	0.0	0.0	0.0	32.7
30	31.6	11.5	27.4	12.7	0.0	35.3	81.7	26.1	28.3	20.0	26.0	48.6
60	38.2	17.9	38.4	38.6	25.4	45.8	88.0	46.5	37.1	43.5	38.5	53.9
90	45.6	23.3	49.5	55.6	39.8	59.2	97.2	60	48.2	56.9	40.6	69.3
120	55.6	45.5	68.2	66.6	49.3	68.6	97.7	71.2	60.9	67.6	65.2	81.3
150	63.2	54.7	78.5	74.5	58.2	79.3	97.4	83.2	72.0	79.0	78.1	90.3
180	74.7	72..4	82.0	82.3	68.2	86.2	97.8	89.0	86.2	84.3	83.2	95.3
210	85.6	83.2	93.0	92.4	79.8	94.0	97.9	93.4	95.3	92.2	95.1	99.1
240	94.0	94.5	97.3	94.8	93.4	95.3	99.0	97.9	99.4	98.9	100	99.9

Table 2(c): Percentage Diclofenac Sodium Dissolved at pH 6.5 and 7.0.

Time	pH 6.5						pH 7.0					
(min)	D1	D2	D3	D4	D5	D6	D1	D2	D3	D4	D5	D6
15	54.2	4.7	25.3	0.0	0.0	36.3	54.3	25.0	26.3	21.7	25.4	35.1
30	77.7	22.4	40.2	39.6	25.6	49.0	65.6	46.9	38.2	35.7	39.7	46.2
60	83.2	42.3	51.2	44.6	39.2	53.9	72.9	57.6	47.2	55.2	49.8	52.1
90	88.9	56.7	62.1	56.6	58.1	69.3	77.9	69.0	58.5	67.3	60.4	67.2
120	93.6	72.5	74.9	67.0	67.2	81.3	82.3	74.5	67.2	76.0	71.0	78.5
150	96.9	83.2	83.5	78.6	76.2	90.3	89.0	88.9	74.1	86.7	82.5	82.5
180	97.2	88.9	91.2	86.2	85.5	95.3	90.1	96.4	85.1	92.6	91.3	90.2
210	98.8	96.6	93.5	95.6	95.5	99.1	95.6	97.9	95.9	95.9	95.2	95.2
240	99.9	99.9	99.9	98.6	99.0	100	99.1	100	99.0	97.1	100	99.7

contents within four hours of testing at the pH range specified as intestinal pH range i.e. between 5.5 and 7.0. There was a wide variation in the rate of drug release at any particular pH. To make the comparison of test formulations easier, Hixon and Crowell [1931] cube root law was used to determine the dissolution rate constants for every brand at every pH on which it was tested.

Hixon and Crowell equation takes into account the changing surface area of the dissolving molecule. Mathematical form of Hixon and Crowell cube root law is given as follows:

$$W_0^{1/3} - W^{1/3} = k\,t \qquad (1)$$

where k is cube root dissolution rate constant.

For the calculation of "k", percent dissolved of diclofenac sodium is subtracted from 100% to get the percentage of the drug that remained undissolved. The percentage of undissolved diclofenac sodium is then converted into grams (W) and used to compute "k" by using Eq. (2)

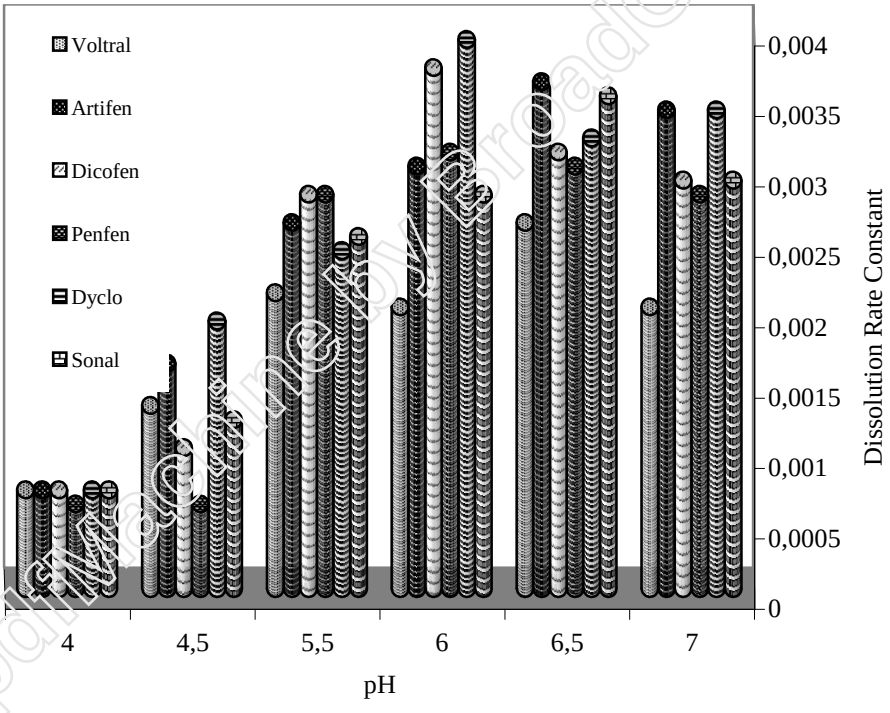

Fig. 1: Cube Root Dissolution Rate Constants for various Diclofenac sodium tablets.

$$1 - W^{1/3} = k\,t \qquad (2)$$

Cube root dissolution rate constants for all t-he six brands at the pH studied were calculated and the results are given in Fig. 1.

It is evident from Fig.1 that voltral has the lowest dissolution rate constant at four of the six pH tested and thus can be declared least bioavailable in

terms of rate of absorption. It can also be seen that change in pH of the dissolution medium affected the drug release behaviour of all the six brands of enteric-coated diclofenac sodium tablets. As pH of the dissolution medium increased, the value of the dissolution rate constant and hence the dissolution rate also increased. The release of drugs from enteric-coated tablets is highly dependent on the pH of the buffer solution [Hayashi *et al.* 1970].

At any particular pH, the difference in dissolution rates among the brands may be due to the use of different coating materials by different manufacturers. Commonly used enteric coating materials are: cellulose acetate derivatives such as cellulose acetate phthalate (CAP), hydroxy propyl methyl cellulose (HPMC) and the two grades of hydroxy propyl methylcellulose phthalate; HP-50 and HP-55, polymethacrylate polymers (Eudragit L and Eudragit S), polyvinyl acetate phthalate (PVAP).

All the enteric coatings in current use possess ionizable acid groups, usually a free carboxylic acid. The equilibrium between unionized insoluble polymer and ionized soluble polymer will be determined by the pH of the medium and pKa of the polymer. Spitael *et al.* [1977 and 1980] observed that dissolution of CAP and Eudragit films is directly proportional to the concentration of the basic salts in the dissolution medium and a linear relationship is reported between dissolution rate and pKa of the basic salts. As the pH of the dissolution medium increases, the coating materials ionize and start breaking and dissolving which cause release of the drug. At lower pH, however, the polymer remains unionized and the integrity of the film is maintained. Davis *et al.* [1986] studied the dissolution profile of enteric coated materials and reported that pKa of the film former and nature of the polymer backbone are the two most important factors that cause variation in the dissolution behaviour of film formers. They graded the enteric coating materials with respect to their resistance to the gastric dissolution media as follows:

CAP > PVAP > HP55 > HP50.

Ranjha [1997] studied the performance of pH sensitive non-cross linked polymers as gastric resistant coating materials. The two selected samples vinyl acetate-co-acrylic acid, VAC/AA molar ratio 60:40 and vinyl acetate-co-crotonic acid, VAC/CA molar ratio 70:30 were used as coatings on rapidly disintegrating cores with a film thickness of 3 mg/cm^2. These coated cores were tested in 0.1N HCl (pH 1.2). In the case of VAC/AA all the cores disintegrated within 30 minutes, while in the case of cores coated with VAC/CA films, two disintegrated within two hours while four did not disintegrate within this period. During the study, film thickness was found to be a major factor affecting the degree of resistance offered by the enteric films to the gastric simulated dissolution medium and this effect of film thickness can be compared with the results of Murthy *et al*. [1986] who suggested that by increasing film thickness, resistance to gastric films also increases. Delporte and Jaminet [1987] reported linearity

between disintegration time and thickness (expressed as mg/tablet) of CAP films on acetyl salicylic acid tablets. Numerous other factors can play their part in causing the observed variation in drug release behaviour. These factors include the amount of diluent used, as Levy [1963] reported that increasing starch content from 5% to 20% resulted in a three- fold increase in the dissolution rate of tablets. Deshpande and Dangre [1987] reported that plasticizers added to the coated material may considerably modify the mechanical properties and permeability characteristics of the film. They reported that higher plasticizer was always associated with faster disintegration time (1.5% & 6% propylene glycol on CAP films). The difference found in the dissolution and disintegration time of these formulations may also be attributed to the inclusion of the excess amount of the hydrophobic lubricants and glidants like magnesium sterate and talc. Size, age and moisture content of the granules, compression force and other processing factors may also affect the dissolution behaviour of different brands.

The value of cube-root dissolution rate constant for Voltral, Artifen, Penfen, Sonal and Dicofen at pH 7 and for Dyclo at pH 6.5 and 7 are low as compared to their value at other pH. The exact reason for this is not known and it needs further investigation.

CONCLUSIONS

Variation in dissolution behaviour of the brands tested may be due to any of the factors discussed above but it can clearly be concluded from the data in Tables 2(a), 2(b) and 2(c) that the enteric coating is greatly affected by change in pH of the dissolution medium. As the pH increases, the dissolution becomes rapid and as the pH of the dissolution medium decreases, the dissolution becomes slow.

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