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DISSOLUTION BEHAVIOUR OF COMMERCIALLY AVAILABLE ENTERIC-COATED ASPIRIN TABLETS

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Abstract: The dissolution behavior of five commercially available brands of enteric coated aspirin tablets were studied, both in 0.1N HCl adjusted to pH 1.2 and phosphate buffer solutions of pH 4.0, 5.0, 5.5, 6.5, 7.0 and 7.5 using USP dissolution apparatus II (paddle method). The drug concentration in dissolution media was determined spectrophotometrically at respective λ_{max} i.e. 276 nm for pH 1.2 and 4.0, 268 nm for pH 5.0 and 5.5 and 266 nm for pH 6.5, 7.0 and 7.5 solutions and the data were analyzed by cube root law. Study has revealed that dissolution rate increases with increase in pH of dissolution medium. At intestinal pH Loprin and Anaprin have fastest disintegration and dissolution followed by Ascard and Anaprin. Nu-Seals failed to release appreciable quantity of drug even at intestinal pH. It has been suggested that possible reasons for difference in dissolution behavior are the difference in the film coating material, techniques and the quantity of hydrophobic excepients employed by different manufactures, which retard penetration of dissolution medium and ultimately decrease availability of drug in the solution.

Keywords: Aspirin, dissolution, enteric coating, hydrophobic excepients, tablets.

INTRODUCTION

Aspirin is non-steroidal anti-inflammatory drug that is frequently used as analgesic, antipyretic, anti-inflammatory and to inhibit platelet aggregation. Aspirin has pKa of 3.5, rapidly absorbs from stomach and upper small intestine. The acidic medium in the stomach keep large fraction of drug in nonionized form, promoting its absorption. However when high concentration of drug enters into mucosal cells, the drug may damage the mucosal barrier and cause gastric upset [Katzung 1992]. Enteric-coated formulations of aspirin are free from this problem. The purposes of an enteric coating are: protecting the drugs from being destroyed by the gastric contents (enzymes or highly acidic gastric fluid), preventing or reducing nausea and vomiting associated with irritation of drugs to gastric mucosa, delivering the drugs to its absorption site in the intestine in controlled and concentrated form.

An enteric coating is a pH sensitive coating that is resistant to stomach contents disintegrates in intestinal contents and releases the drug in the small intestine after disintegration. Most enteric-coated dosage forms are in the form of tablets and release the drug by disintegration and dissolution.

When drug is administered orally in tablet dosage form, the rate of absorption is often controlled how fast a drug disintegrates and dissolves from its intact dosage form in GIT. In other words dissolution is often rate limiting step in absorption. Therefore, dissolution rate can affect onset,

intensity, duration of response and overall availability of drug from dosage form [Wagner and Pernarowaski 1971].

Dissolution kinetics may be influenced by physico-chemical characteristics of the drug, the formulation factors and the biological factors [Shargel and Andrew 1985].

Dissolution profile of a solid dosage form serves as an important test to assure the quality of a drug product. Dissolution is now accepted as an in vitro standard for drug release from conventional dosage forms. The use of such tests to determine drug product bioavailability or bio-equivalence has been advocated by United States Food and Drug Administration [Gibaldi 1984].

The purpose of this study is to compare the dissolution behavior of some commercially available brands of enteric-coated aspirin tablets in Pakistan.

MATERIALS AND METHODS

MATERIALS

- The formulations examined comprised of 75 mg compressed enteric-coated tablets with brand names of Ascard, Loprin, Nu-Seals, Massprin and Anaprin. All of these were purchased from local market. The same batches of tablets were used throughout the study. Their technical data are given in Table 1.
- The reference standard pure aspirin powder was purchased from Sarco Chemical Industries, Multan, Pakistan.
- Deionized distilled water (pH 5.8 $\pm$ 0.2 as measured by Orion pH meter model 301) obtained from all glass electrically heated still and stored in well stopered five liter glass flask, was used throughout the study.
- Fuming hydrochloric acid 37% extra pure (density 1.19 g ml^{-1}) supplied by Fluka AG chemicals, was suitably diluted and used as dissolution medium.
- Potassium Hydrogen Monophosphate (KH_2PO_4) and Sodium Hydroxide (NaOH) of analytical grade were used for preparing buffer solutions of different pH.
- Standard dilutions ranging from 1-10 mg per 100ml of pure aspirin powder were prepared in first 0.1N HCl adjusted to pH 1.2 and then in phosphate buffer solutions of varying pH ranging from 4 to 7.5. The λ_{max} was calculated by using 5mg per 100ml dilution sample of pure aspirin at each pH 1.2, 4.0, 4.5, 5.5, 6.5, 7.0, 7.5 by using double beam UV spectrophotometer Spectronic Genesys HM 5 model cat. No. 336090.20 having 128K-memory soft card.
- The USP dissolution apparatus, paddle method (apparatus II) having six beakers in joint assembly was used in dissolution testing.

Table 1: Average technical data of five brands of enteric-coated aspirin tablets

Brand Name	Manufacturer	Batch No.	Weight (gm)	Disintegration time in min.		Assay %
				pH 1.2	pH 7.0	
Anaprin	Opal Labs	03948	0.154	No disintegration within two hours	40	99.16
Ascard	Atco Labs.	9D029	0.199		50	97.27
Loprin	Highnoon	2948	0.186		15	100.36
Massprin	Mass Pharma	8845	0.182		20	103.86
Nu-Seals	Elli-Lilly	135A	0.177		120	95.60

METHODS

The dissolution test specified in USP for delayed release (enteric-coated) dosage form was conducted on all five brands of enteric-coated aspirin tablets using apparatus II (method B) at speed of 75 rpm. The dissolution medium was, first, 900ml of 0.1N hydrochloric acid and then phosphate buffers of pH 4.0, 5.0, 5.5, 6.5, 7.0 and 7.5.

During the test run, samples (10 ml in size) were withdrawn from dissolution vessel at specified time intervals and volume of medium was kept constant by addition of dissolution medium after each sampling. The absorbance was measured at 276 nm for pH 1.2 and 4.0, 268 nm for pH 5.0 and 5.5 and 266 nm for pH 6.5,7.0 and 7.5 solutions on the same spectrophotometer that was used for measuring the absorbance of standard aspirin solutions to calculate the total contents of aspirin in the sample.

RESULTS AND DISCUSSION

The percentage dissolved of active ingredient at specified time intervals were calculated both in 0.1N HCl adjusted to pH 1.2 and buffer solutions of pH 4, 5, 5.5, 6.5, 7 and 7.5. The results are presented in Table 2.

The analysis of data given in Table 2 proved the existence of significant difference of drug release from each formulation by changing the pH of the medium. Dissolution of Loprin and Mass-prin is the fastest i.e. 82% and 76% within 2 hours at pH 7.0 and 90% and 80% at pH 7.5. The dissolution of Ascard and Anaprin is slower i.e. both dissolved 50% within 2 hours at pH 7 and 97% and 73% at pH 7.5. On the other hand Nu-seals shows only 20% dissolution at pH 7 and 21% at pH 7.5.

The data were further analyzed by applying Crowel and Hixon Cube Root Law [1931] represented by following equation:

$$W_0 - W = K\,t \qquad (1)$$

where W_0 is amount of drug at zero time, W is amount of undissolved drug at time t and K is cube root dissolution rate constant in $(\text{weight})^{1/3}$ per time.

To calculate the cube root dissolution rate constant, percent dissolved of aspirin is subtracted from 100% reported as percent assayed to get percent undissolved (W), the quantities are changed into grams and computed into cube root using equation (3).

$$\sqrt[3]{1} - \sqrt[3]{W} = K t \quad (2)$$

$$1 - W^{1/3} = K t \quad (3)$$

The calculated cube root values were plotted against time (min). The cube root constants for five preparations were calculated from slops of their plots and represented in Fig. 1. Dissolution of Ascard, Loprin and Massprin showed the dependency on pH of dissolution medium, as the pH of medium increases the dissolution rate also increases. Hayashi *et al.* [1970] also reported that dissolution rate increases by increasing pH and ionic strength of buffer solution.

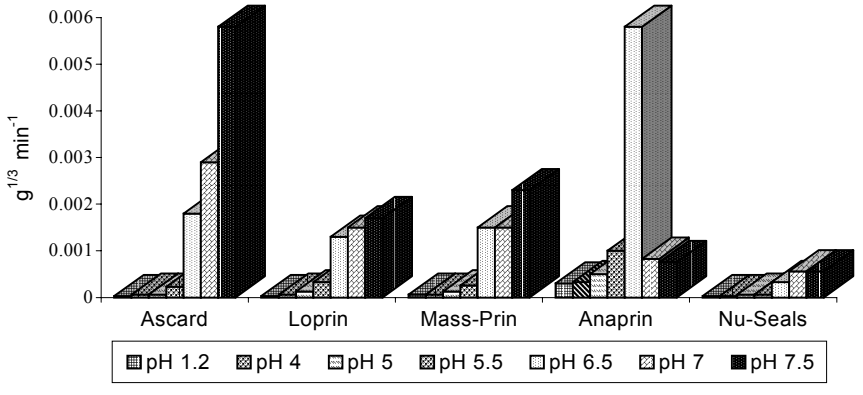
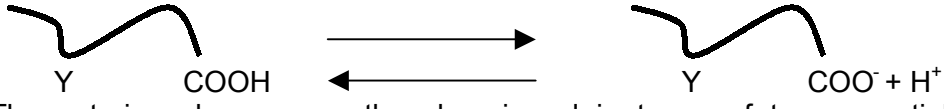


Fig. 1: Cube root dissolution rate constant of various enteric-coated aspirin tablets at different pH.

Anaprin and Nu-Seals showed the similar results, except that Anaprin showed fastest dissolution at pH 6.5 and Nu-Seals at pH 7.0, which may possibly be due to difference in nature of coating material.

Commonly used coating materials for enteric-coating are: (1) cellulose derivatives such as cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP, Two grades HP-50 and HP-55), (2) polymethacrylate polymers (Eudraget S and Eudraget L), (3) polyvinyl acetate phthalate (PVAP).

All the enteric polymers in current use possess ionizable groups, usually a free carboxylic acid group. The enteric polymers in the unionized state are hydrophobic and water insoluble, but in the ionized state they are water-soluble. The dissolution process can be generally presented as follows:



The enteric polymers can thus be viewed in terms of two essential components: a solubilizing group COOH and a hydrophobic group Y. The pH of the medium and the pK_a of the polymer will determine the equilibrium between unionized and ionized polymer [Heller *et al.* 1978].

Murthy *et al.* [1986] evaluated coating levals required for gastric resistance of three commercially available Eudragit L 30 D, Aquatric and Coateric polymers. They reported that by increasing the film thickness resistance to gastric fluid increases. It is suggested the minimum coating thickness that provides suitable gastric resistance for two hours is 10 mg cm^{-2} Aquatric, 12 mg cm^{-2} Coateric and 2 mg cm^{-2} Eudragit L 30 D.

Table 2: Percentage of Aspirin dissolved in dissolution medium at different pH and time (min).

pH / t (min)	1.2	4.0	5.0	5.5	6.5	7.0	7.5
			Ascard				
30	0	0	0	0	0	0	20.0
60	0	0	0	0	0	20.0	40.0
90	1.93	6.5	14.5	14.5	14.5	25.0	64.0
120	2.20	6.8	15.0	19.0	15.0	50.0	97.0
150	2.26	8.20	16.7	21.5	19.0	59.0	97.0
180	2.28	8.5	17.0	26.0	40.0	76.0	97.0
240	3.19	9.5	18.1	23.0	98.0	96.5	98.0
			Massprin				
30	0	0	0	5.0	61.0	60.5	71.0
60	0	0	2.5	10.5	76.0	75.0	78.0
90	0.98	4.2	4.5	20.0	76.5	75.5	79.0
120	2.85	5.8	8.0	32.0	76.5	76.0	79.5
150	2.90	7.5	10.5	33.5	77.5	76.5	80.0
180	2.95	7.8	11.3	36.0	78.0	77.0	83.0
240	3.16	8.6	19.2	41.6	78.5	80.0	90.0
			Loprin				
30	0	0	4.5	12.5	30.0	34.5	50.0
60	2.45	0	6.5	20.0	52.0	62.0	70.0
90	3.30	0	9.8	22.5	70.0	70.0	80.0
120	3.55	9.3	10.0	26.0	78.0	82.0	90.0
150	3.58	9.5	11.6	32.0	78.5	83.0	92.0
180	3.61	9.5	12.0	32.5	78.5	83.5	93.0
240	3.65	10.6	19.5	38.5	80.0	86.0	96.0
			Anaprin				
30	0	0	0	0	10.0	20.0	30.0
60	0	0	0	4.0	19.5	34.0	52.0
90	0	5.0	7.2	7.5	30.0	38.5	60.0
120	2.30	5.12	14.5	19.5	30.0	50.0	73.0
150	2.45	5.12	16.0	20.0	41.0	58.0	80.0
180	2.58	5.12	17.5	36.5	49.0	76.0	82.0
240	8.45	11.5	20.1	38.5	79.0	83.0	90.0
			Nu-Seals				
30	0	0	0	0	0	8.0	8.0
60	2.45	0	3.0	5.0	9.0	18.5	18.5
90	2.46	0	3.5	5.0	10.0	18.5	20.0
120	2.48	0	4.3	5.0	10.5	20.0	21.0
150	2.52	1.45	4.6	5.5	12.0	21.5	21.0
180	2.55	2.62	5.0	8.0	12.0	22.0	31.0
240	2.65	3.28	6.0	9.5	18.0	35.0	32.0

Davis *et al.* [1986] identified pK_a and backbone structure affecting the dissolution behaviour of various phthalates containing enteric polymers. The dissolution rate profile of HP-50 was found to be shifted 0.3-0.4 units below than HP-55; obviously the same difference exists in their pK_a values. The pK_a values; for HP-50 is 4.20 and HP-55 is 4.47. Backbone and substituted groups affect the hydrophilicity and hydrophobicity of the polymers and therefore affect the dissolution behaviour of the polymers. Plasticizers are added to polymeric substances because they reduce brittleness, improve flow, impart flexibility, increase toughness and tear resistance. The mechanism by which the plasticizers achieve these changes might be reduction in cohesive forces of the polymeric molecules that causes a decrease tensile strength, a lower softening temperature and a decrease in the glass transition temperature. Some commonly used plasticizers are: phthalate esters, phosphate esters, fatty acid esters and glycol derivatives.

Spitael and Kinget [1977] determined the effect of various plasticizer on the CAP film permeability to HCl and to caffeine. The concentration of the plasticizer was 20% w/w of the amount of the polymer. They observed that polyethylene glycol increases the permeability while diethyl phthalate and acetyltriethyl citrate do not have any significant effect on the film permeability.

Lachman and Drubulis [1964] determined the effect of varying concentration of triacetin, diacetin, diethyl phthalate, dimethyl phthalete, citroflex-2, citroflex-A2 and dibutyl tartrate plasticizers on the water vapour transmission (WVT) of CAP free film. It is reported at first a decrease followed by an increase in WVT through the film by increasing the concentration of the plasticizer. For explanation they suggested that the lower concentration of the plasticizer is used for filling the interstices of the polymer, but further addition of the plasticizer would have only dilution effect on the polymer. It is also observed that WVT was directly proportional to the relative humidity for both lower and higher plasticizer concentrations.

The permeability of the film depends on the nature of the plasticizer and nature of the polymer. Higuchi and Aguiar [1959] prepared films of various cellulose esters and studied the water vapor permeability through these films. They reported that the rate of permeation through the films of cellulose esters is primarily governed by the availability of polar groups because in a more polar film, the affinity of the water molecules for the barrier phase is greater and hence permeability coefficient will be increased.

The difference found in disintegration and dissolution can also be due to inclusion of excessive hydrophobic lubricants and glidants during the compression of tablets. Hydrophobic lubricants and glidants would form the hydrophobic film around the granules thus increasing contact θ

(between solid and liquid) more than 90 degree resulting in poor wettability of tablet.

CONCLUSIONS

There are two forces cohesive and adhesive that operates during film formation. The force involved between the film-forming polymer molecules is called cohesive, while the force operated between the film and substrate is called adhesive. The cohesive forces are related to the shape of polymeric molecules, crystallinity, polar groups along the polymer chain, regularity of the chain structure, branching, molecular weight, and molecular weight distribution.

By taking into account these preliminary experiments, it can be predicted that Loprin and Massprin would be approximately bioequivalent, while tablets Ascard and Anaprin will have delayed bioavailability and tablets Nu-Seals will be less bioavailable. Use of different enteric coating materials, method of their application and excessive amount of hydrophobic lubricants are probably most likely candidates responsible for retarded dissolution in Ascard, Anaprin and Nu-Seals. However, further studies would be required for comparison of bioavailability of these formulations on human volunteers.

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