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EFFECT OF SOME FORMULATION ADDITIVES ON THE ORAL ABSORPTION OF INDOMETHACIN.

J.K.Pandit, G.Jagadeesh, M.Nagabooshanam & M.K.Tripathi

Department of Pharmaceutics, I.T., Banaras Hindu University, Varanasi -221 005 India.

ABSTRACT

Higher dissolution rates of indomethacin were noted in glycerin-water mixtures, sucrose solutions, sod.-cmc mucilage, from a fabricated capsule containing a buffer and also from drug crystals obtained by precipitation in presence of a physiological surfactant solution. Dogs fed with the drug along with these additives and in the form of a lipid-containing dosage form showed significantly increased plasma-indomethacin levels. The magnitude of plasma-drug levels from aqueous and oily suspensions and from the prepared capsule was found to be significantly greater than that obtained from the marketed preparation.

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INTRODUCTION

Limited solubility of drugs has always presented a problem in pharmaceutical formulation of a drug. The extent of bioavailability of an insoluble drug is controlled by its dissolution rate in the GI fluid (1). The bioavailability, moreover, can vary widely between different dosage forms of the same drug (2-8). Articles of food and dosage form variables considerably affect the bioavailability of a drug (9-15). The absorption of indomethacin, a non-steroidal anti-inflammatory drug with a very low aqueous solubility (0.01 mg/ml) is reported to be formulation dependent and this drug has been classified under drugs showing clinical inequivalence among its formulations (16,17). The solubility of indomethacin in PEGs 400 and 600 is reported by Krasowska et al (18) to be the best out of some selected solvents, and its solubility has been reported to be dependent on the mw of the PEG used (PEG 400,600,1000) (19). The possible effect, if any, on the plasma levels of indomethacin fed in presence of PEG 400 was studied. Physiological surfactants such as bile salts and lecithin play an important role in the intestinal absorption of poorly soluble drugs (20-24). There is no report describing the effect of exogenous bile on the absorption of indomethacin. The dissolution and

absorption characteristics of the drug precipitated in presence of a bile salt (sodium taurocholate, stc) was studied. It has been reported (25) that the dissolution and absorption of drugs is influenced by polyelectrolytes like sodium-cmc and water-miscible or aqueous vehicles e.g., glycerin and syrup. These two categories of suspension-additives were studied for their possible effect on indomethacin absorption.

The absorption of indomethacin has been reported to be enhanced in presence of a buffer (26). Moreover, there are reports (11,13) that for a lipophilic, poorly water soluble drug, the bioavailability can increase if it is administered in a lipid-containing dosage form. On these premises, two dosage forms, one a capsule containing indomethacin and trisodium phosphate, and another, an oil suspension, were fabricated and the plasma levels evaluated in comparison to the plasma levels attained by a marketed capsule (Idicin, IDPL, containing 25 mg of Indomethacin BP/Cap.), and an aqueous suspension, respectively.

MATERIALS AND METHODS

Indomethacin (Lot 437/AIM, IDPL, Hyderabad, India), PEG 400, stc, sucrose, glycerin and sodium-cmc (Nymcel ZSB-16, Nyma b.v., Holland) were obtained from commercial sources and used as received. All

other chemicals were of analytical grade. Unless otherwise stated, the drug was sieved to yield particles in the range of 100-150 μm.

Dissolution rate determinations

The dissolution rates were determined according to the method of Levy and Hayes (27), with slight modification, in 500 ml of the respective dissolution medium at 37±0.5°C. An appropriate amount of the powder sample equivalent to 100 mg of indomethacin was used for dissolution rate studies. Samples were withdrawn through a filter as a function of time and analysed for drug content. The dissolution medium was replenished after each sampling to maintain a constant volume. Dissolution rate from capsules was studied by the method of Goodhart et al (28). Each experiment was performed in triplicate.

Crystallization of Indomethacin in Presence of stc

To a saturated solution of indomethacin in ethanol 10, 20 and 30 mM aqueous solutions of stc were added till there was no further precipitation of the drug crystals. The recrystallized drug was recovered by filtration, blotted to remove excess liquid and dried in vacuum desiccator. The drug crystals thus obtained when assayed for drug-content were found to

conform to pharmacopoeial limits. No shift in the mp of the treated drug was observed.

Preparation of dosage forms

25 mg each of indomethacin and trisodium phosphate were mixed intimately and filled in hard gelatin capsules in a hand capsule filling machine. The filled capsules conformed to weight and content uniformity tests. For the aqueous and lipid containing dosage forms, 100 mg indomethacin was triturated gently either with 0.2% sodium-cmc mucilage or sesame oil, and the volume made up to 25 ml. The suspensions were formulated to contain 10 mg of polysorbate-80 as dispersing agent.

Assay procedures

The dissolution rate samples were assayed for indomethacin in a 1:9 mixture of 1 N HCL and spectroscopic methanol at 318 nm in a spectrophotometer. All plasma levels were determined by the spectrofluorometric method of Hucker et al (16).

Protocol in dog studies

Healthy mongrel dogs of either sex weighing 10-12 kgs were conditioned for 72 hrs to the animal house, and were maintained on a standardized animal food. The animals were fasted with water ad libitum, for 12 to

14 hrs prior to experiments and 12 hrs post-experiment. Indomethacin (100 mg) along with 25 ml of the respective medium (20% w/v soln.of PEG 400, 20% sucrose solution, 15% glycerin solution or sod. cmc 0.5%), or four capsules (fabricated and marketed), or the stc-treated drug (equivalent to 100 mg of indomethacin) or 25 ml of either aqueous or oily suspension, was fed to the animals. For the control, 100 mg of drug powder was fed directly. Fifty ml of luke-warm tap water was then given to the animals. The animals were observed constantly to make sure that there was no vomiting. At least five animals were used for each parameter. Blood samples (3 ml) were collected at 0, ½, 1, 2, 4, 8 and 12 hrs post-administration, and assayed for plasma-drug content. The dosing with additives was done in a completely randomized manner. There was a 2 week interval between doses of the drug, during which time the drug plasma levels fell to undetectable levels.

RESULTS AND DISCUSSION

It is evident that Indomethacin precipitated in presence of all the three concentrations (10,20 and 30 mM) of stc showed significantly ($P<0.05$) increased dissolution rate, with a linear increase with stc concentration. The minute quantity of the bile salt adhering to the drug crystals enhances the dissolution

rate by better wetting, and not by micellar solubilization. The drug obtained with 30 mM stc as precipitant shows a very fast dissolution rate between 20 and 40 min, with a sudden fall thereafter. This is due to a micro-environmental effect, in that in the initial stages of dissolution the drug crystals are surrounded by a concentrated layer of drug-solution, dissolved due to the adhering surfactant. Further agitation of the medium removes the solubilized drug layer and some of the drug is thrown out of solution.

The rate and extent of indomethacin dissolution was significantly higher ($P<0.05$) in glycerin, sucrose and sod.cmc. The better dissolution is rhought to be due to better wetting of the drug particles. As earlier reported by Paruta and Sheth (29) that sucrose solutions differ in their dielectric constants, this factor may be accounted for the better dissolution in sucrose solutions. IR examination of the drug particles recovered from the dissolution medium ruled out any possibility of soluble drug-additive complex formation. A five-fold increase in dissolution is noted from the buffered capsules over the marketed capsules at 60 min. The amount of buffer present in the capsule did not affect the pH of the dissolution medium, the increased dissolution being effected by the buffer component only.

Table I
Dissolution Rates of Indomethacin in/from Different Systems

Systems		Average Amount of Indomethacin Released in mg/100ml* (Mean±S.E.)					
		10	20	30	40	50	60
In Distilled water.		0.963±0.02	1.065±0.03	1.168±0.05	1.235±0.05	1.266±0.07	1.371±0.05
From Drug ppted by STC.	10mM	1.593±0.05	1.757±0.05	1.941±0.05	2.052±0.19	2.258±0.16	2.131±0.20
	20mM	1.574±0.05	1.793±0.03	1.848±0.02	1.941±0.07	2.552±0.13	2.984±0.13
	30mM	1.352±0.04	1.773±0.05	2.722±0.10	3.244±0.10	2.831±0.10	2.674±0.07
In Glycerin	5%	1.370±0.02	1.626±0.03	1.882±0.07	2.048±0.15	1.920±0.07	1.902±0.02
	10%	2.241±0.07	2.330±0.07	2.490±0.06	2.348±0.10	2.352±0.08	2.356±0.07
	15%	2.000±0.03	2.113±0.05	2.559±0.10	2.473±0.05	2.201±0.05	2.223±0.02
In Sucrose	10%	1.593±0.02	1.667±0.04	1.978±0.06	2.090±0.02	2.223±0.02	2.404±0.07
	15%	1.704±0.05	1.906±0.07	1.962±0.07	2.074±0.07	2.242±0.03	2.449±0.08
	20%	1.852±0.05	2.537±0.08	2.525±0.08	2.476±0.12	2.833±0.08	2.768±0.11
In Sodium-cmc.	0.25%	2.981±0.07	5.826±0.29	10.568±0.12	11.026±0.24	11.616±0.43	11.450±0.53
	0.50%	7.611±0.31	10.650±0.30	12.820±0.38	14.975±0.46	16.566±0.11	17.431±0.05
	0.75%	4.592±0.32	6.059±0.14	8.229±0.18	9.087±0.14	9.508±0.24	10.117±0.21
From Fabricated Capsule.		18.463±0.49	19.259±0.16	19.671±0.09	20.123±0.10	20.080±0.07	20.280±0.11
From Marketed Capsule.		3.148±0.05	3.550±0.05	3.789±0.06	4.215±0.03	4.682±0.08	4.301±0.03

* Mean of 3 readings

In the absorption studies a better availability i.e., increased rate and extent of absorption is observed with 20% PEG 400 solution, which is due to a solvent effect of the polymer on the drug and also due to precipitation of the drug in microform in the stomach.

A significant increase ($P<0.05$) in the Cmax for PEG 400 was observed in comparison to the control, The stc-treated drug although showed an increased rate of absorption, the extent of absorption is essentially identical to that of the control ($P>0.05$). As Anello and Levy (30) have reported that pre-CMCs of surface-active agents enhance drug transfer by a direct effect on the biologic membrane and not by interacting with the drug, the minute quantity of stc present in the drug crystals did not affect the intestinal mucosa significantly, hence there was no significant difference in the extent of absorption from the stc-treated drug. The availability from glycerol, sucrose and sodium-cmc is not different from the control ($P>0.05$). The higher viscosity of 0.5% sodium-cmc delays gastric emptying and hence it may be safely concluded that the observed slower absorption rate is due to the slower rate of movement of drug molecules to the absorbing membranes. The low availability from the marketed

TABLE II

Biologic availability parameters of Indomethacin absorption from different systems

Systems	C_{max}*, mg% ± S.E.	T_{max}, hr.	AUC, 0–12hrs, mg- h/L
Control	0.317 ± 0.019	8	103.7
PEG400, 20%	0.520 ± 0.023	1	167.7[a]
Drug ppted by stc, 30mM	0.383 ± 0.008	1	124.1[b]
Glycerin, 15%	0.321 ± 0.011	4	148.8[b]
Sod.cmc, 0.05%	0.355 ± 0.017	4	150.4[b]
Sucrose, 20%	0.324 ± 0.009	4	119.1[b]
Marketed capsule	0.225 ± 0.009	2	76.5
Fabricated capsule	0.340 ± 0.020	1	117.3[c]
Aqueous suspension	0.569 ± 0.016	2	186.7
Oily suspension	0.810 ± 0.031	1	193.3[d]

*Average of 5 readings; a, $p < 0.05$; b, $p > 0.05$; d, $p < 0.05$ between aqueous and oily suspension; c, $p < 0.05$ between marketed and fabricated capsule.

capsule seems to be due to delayed deagregation and dissolution of the capsule contents.

The prepared suspension is better in performance than both the marketed capsule and the control, this effect being due to a better dispersal of the drug in the suspension. The oily dosage form shows considerably improved absorption, which is in conformity with similar finding by other workers (31-33) in that high fat concentrations stimulate the bile flow into the small intestine, which enhances the dissolution and absorption of the poorly soluble drug. Although high fat diets are reported to slow down gastric emptying, the Tmax observed with the oily suspension is the same as with the aqueous suspension. This is presumably due to quick passage of the low-bulk dosage form from the fasted stomach.

Since the toxic effects are dependent on the gut-retention time, administration of indomethacin along with a buffer or in the form of a lipid-containing preparation will result in a quicker disappearance of the drug from the gastric environs, which may lessen the serious toxic effects of this drug. As a result of this study in dogs, the effect of concurrent administration of the additives on the absorption of indomethacin in humans are being investigated.

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