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STUDIES ON PHTHALIC ACID-PROPANE-1, 2-DIOL-GLYCEROL CO-POLYESTER AS AN ENTERIC COATING MATERIAL

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ABSTRACT: Enteric coating material that, was synthesized in the laboratory and applied to a tablet and also drug release profile was investigated. A polymeric material - Phthalic acid propane-1,2 diol-glycerol co-polyester (PPGC) was synthesized from phthalic acid and propane-1, 2-diol with 5% glycerol of total weight as a crosslinking agent using Dean-Stark apparatus with Ferric Chloride as catalyst and o-xylene as the reaction medium. The polymer was dissolved in volatile organic solvent (Ethyl acetate) to prepare coating solution. The coating solution was sprayed over the DS tablet in a small coating pan with continuous hot air flow. The coating pan was allowed to rotate until the solvent evaporated and the tablet dried. The percentage of drug release from di-chlofenac sodium (DS) core and coated tablets (coated by phthalic acid-propane-1, 2-diol-glycerol co-polyester) instimulated gastric fluid (pH = 1.2) and in stimulated intestinal fluid (pH = 7.4), was investigated and according to B.P. standard drug release profile was obtained.

INTRODUCTION: The synthesis and development of biodegradable polymer is one of the leading frontiers of research in polymer science of present time. Linear polyester such as poly lactic acid, poly glycolic acid etc. and network polyesters such as citric acid glycerol co-polyester are biodegradable and they are used for specialized applications, such as controlled drug formations, insecticide, pesticide and fertilizer carries as well as nontoxic surgical implant materials.

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Tablet coating is recently a moderation of tablet formulation. Coating may be done defined as the process of compressing a granulating layer around the performed tablets. It is an additional step for manufacturing of tablets. Tablets are originally for the sake of pharmaceutical elegance by improving appearance, test and solubility. More recently coating has been used to control the site of drug release (Enteric coating) [1, 2, 3] and delay or prolong the release of drug from the dosage form (sustained action) hence the absorption of drug present.

The nature of coating varies; it may be simple or complex. In its simplest form it may merely consist of a thin film of varnish, applied to make the tablet dust free and reduce any bitter taste. In most complex form it may consist of inner and outer

shell enclosing differ types of drugs [4, 5] which may be incompatible or are required to be released at a specific time.

Enteric coating is applied to the tablet to protect the tablet core from the disintegration in the acid environment of the stomach or to delay disintegration until they reach the upper intestine.
The commercially used materials for enteric coating [6, 7] include fats and fatty acid, shellac and shellac derivative and the cellulose acetate phthalates. Now a day the products so produced are gradually coated with cellulose acetate phthalates because they give most satisfactory enteric coatings.

For this we have taken up the project to synthesize a biodegradable polymer (Phthalic acid propane-1, 2diol-glycerol co-polyester) and using as an enteric coating material [8, 9].

In the present study our synthesized co-polyester was used as an enteric [10, 11] coating material and the results were investigated.

MATERIALS AND METHOD:

Phthalic acid, propane-1, 2-diol and glycerol were the monomers of the synthesized co-polyester and were purchased from E. Merk Limited, Mumbai (98-99%). Core tablets of diclofenac sodium (DS) 50 mg supplied by Chemico Laboratories Ltd. Rajshahi, Bangladesh. Other chemicals and reagents were of analytical grade. Reference standard of diclofenac sodium (DS)- 99.2% purity used for analytical purpose was obtained from Beximco Pharmaceuticals Ltd. Tongi, Dhaka, Bangladesh.

Instruments & Equipment's:

The following equipment's were used in the investigation

- **i.** Pipette, conical flask, beaker, glass rod etc.
- **ii.** pH meter. (Type: pH-3C, Made by Shanghai Rex Instrument Factory, China)
- **iii.** Electric Balance. (Type: H-51, Metter Instrument Co. - Switzerland)
- **iv.** Tablet dissolution tester. (Type: USP-XXII, Electrolab TDT-01, Made in U.S.A)
- **v.** UV-Spectrophotometer. (Type: UV-VIS Spectrophotometer, U-1800, Tokyo, Japan)

Solution Preparation:

- **i.** Gastric fluid (pH=1.2): 2 gm. NaCl and 7 ml of concentrated HCl was dissolved in distilled water to make 1000 ml solution. The solution was used as the medium of gastric fluid.
- **ii.** Intestine fluid (pH=7.4): 4.303 gm of KH_2PO_4 and 2.583 gm. of Na_2HPO_4 (Dried for 2 hrs. at 110˚C) was dissolved in CO_2 free distilled water. Then the two solution were mixed at the medium of intestine fluid.

Coating Solution Formation:

i) Polymer: Most commonly used polymers for enteric coatings are the derivatives of cellulose such as hydroxyl propyl methyl cellulose acetate, methylcellulose, ethyl cellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, acrylate etc. acrylate based polymers are also used in plain film coatings. However, other types are available in modifications designed to give gastric insoluble films or controlled release properties.

ii) Solvents: Volatile organic solvents such as ethyl alcohol, acetone, ethyl acetate, methyl ethyl lactone, methylene chloride, iso-propanol etc. are used for the dissolving of the polymer.

iii) Plasticizers: The role of plasticizer is to improve the physical properties of the polymer film. One important property is their ability to decrease film brittleness. Commonly used plasticizer includes, PEG, propylene glycol, glycerol and its esters and phthalates esters. In general only water-miscible plasticizer can be used for aqueous based spray system.

iv) Colorants: Coloring agents are used to improve elegance to the tablets. Sometimes they are also used to identify the different types of tablets. The commonly used colors are inorganic- iron oxide and also natural colors- carotenoid, chlorophyll etc.

Preparation of Diclofenac Sodium (DS) Standard Calibration Curve:

For the preparation of standard curve of diclofenac sodium for its quantitative determination in the subsequent experiments, phosphate buffer solution

of pH= 7.4 was used as the medium. Absorbance's of some known solutions of the drug were measured at its λ_{max} (274 nm) on a UV-VIS (Model: U-1800) spectrophotometer. The standard curve (**Fig. 1**) was constructed by plotting the absorbance of the drug against its concentration in the suitable region.

Process Description:

Film coating involves the deposition usual by a spray method of a thin film of polymer surrounding the core tablet. The coating liquid (Solution) contains a polymer in a suitable liquid medium together with other ingredient such as pigment and plasticizer. This solution is sprayed on a rotated mixed tablet bed. The drying conditions permit the removal of the solvent so as the leave a thin decomposition of coating material around each tablet core.

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) with potent anti-inflammatory, analgesic and antipyretic properties. Gastrointestinal disterbances are the major adverse effects associated with diclofenac therapy and thus for oral administration, the drug is usually formulated as enteric-coated tablets. Enteric-coated dosage form release drug in the intestine and has been reported to decrease gastric irritation.

Dissolution Studies:

The dissolution studies for both the core tablets and the coated tablets were performed in order to evaluate the effect of the polymer on the release of the drug. A USP Type-XXII dissolution apparatus (paddle stirrer), Electrolab TDT-01 with a rotation speed of 50 rpm was used for dissolution experiments. A pH=1.2 solution was used as the simulated gastric fluid and a pH=7.4 buffer solution was used as the intestinal fluid. One liter of simulated gastric fluid heated at (37±0.5) ˚C was used initially for the dissolution studies which was replaced after 2 hours by 1000 ml of simulated intestinal fluid heated previously at (37±0.5) ˚C.

Samples (5ml) were withdrawn from the simulated gastric fluid at 30 minutes intervals for 2 hours and from intestinal fluid at 15 minutes intervals, which were immediately compensated with the same amount of fresh medium preheated at (37±0.5) ˚C. The amount of drug dissolved was calculated at 274nm using a UV-VIS (Model: U-1800) spectrophotometer with the help of the calibration curve (**Fig 1**). The *in-vitro* release studies were performed on five coated tablets and one core tablet.

RESULTS AND DISCUSSION:

From the degradation study it was found that, phthalic acid, propane-1, 2-diol-glycerol co-polyester remained intact in the gastric fluid (pH = 1.2) but gradually degraded in intestinal fluid (pH = 7.4). Enteric coating material resists the release of the drug form the core tablet in the gastric environment but it aids drug release in the intestine. In this study, it was found that the polymer did not degrade or swell in the gastric fluid when coated on a core tablet for as long as two hours. (**Table 1, Fig 1).** But in the intestinal fluid it gradually degraded and thereby helped drug release from the core tablet (**Table 2, Fig 2**). The mean (± SEM) present release of DS from the core & coated tablets is given in **Fig. 3** that corresponds to the BP drug release profile from enteric-coated tablets.

So, phthalic acid, propane-1, 2-diol-glycerol co-polyester might be used as an enteric coating material. One of the advantage of this coating material is that, no plasticizer was required to add to the formulation as the polymer itself has got sticky property.

TABLE 1: CALIBRATION OF UV-SPECTROPHOTOMETER FOR DICLOFENAC SODIUM

Concentration of standard diclofenac sodium solution (mg./ L)	Optical Density at 274 nm
5	0.120
10	0.250
15	0.400
20	0.500
25	0.630
30	0.760
35	0.890

40	1.040
45	1.160
50	1.290

TABLE 2 DISSOLUTION OF DICLOFENAC SODIUM (DS) TABLETS IS STIMULATED GASTRIC FLUID (pH = 1.2)

Sample	Percentage (%) of Drug Release			
	Time (30 min)	Time (60 min)	Time (90 min)	Time (120 min)
Core	5.00	15.00	28.00	40.00
Tablet-1	1.00	2.50	3.50	5.00
Tablet-2	0.90	2.40	3.40	4.90
Tablet-3	1.20	2.60	3.60	5.20
Tablet-4	1.30	3.20	4.20	5.50
Tablet-5	2.00	3.80	5.00	6.10

TABLE 3 DISSOLUTION OF DICLOFENAC SODIUM (DS) TABLETS IS STIMULATED GASTRIC FLUID (pH = 7.4)

Sample	Percentage (%) of Drug Release			
	Time (15 min)	Time (30 min)	Time (45 min)	Time (60 min)
Core	62.00	88.00	94.00	95.00
Tablet-1	30.00	55.00	77.00	90.00
Tablet-2	28.00	53.00	75.00	90.00
Tablet-3	27.00	50.00	73.00	88.00
Tablet-4	25.00	48.00	70.00	86.00
Tablet-5	24.00	46.00	68.00	86.00

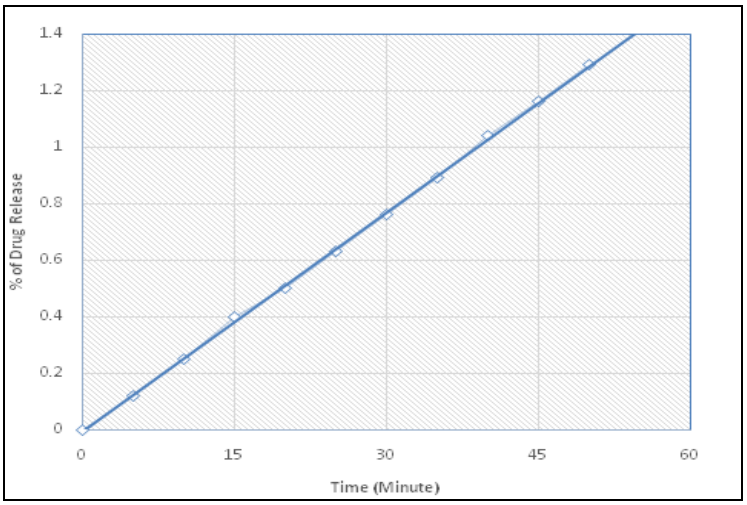

FIG. 1: DICLOFENAC SODIUM (DS) STANDARD CALIBRATION CURVE

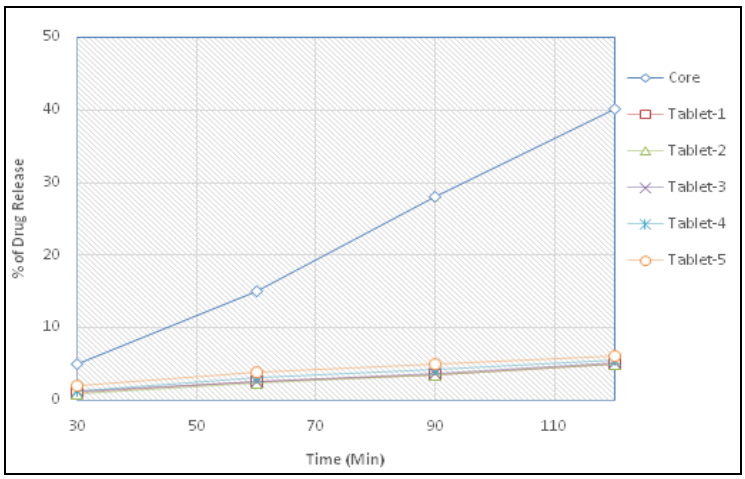

FIG 2 PERCENTAGE OF DRUG RELEASE FROM DICLOFENAC SODIUM (DS) CORE AND COATED TABLETS IN STIMULATED GASTRIC FLUID (pH = 1.2)

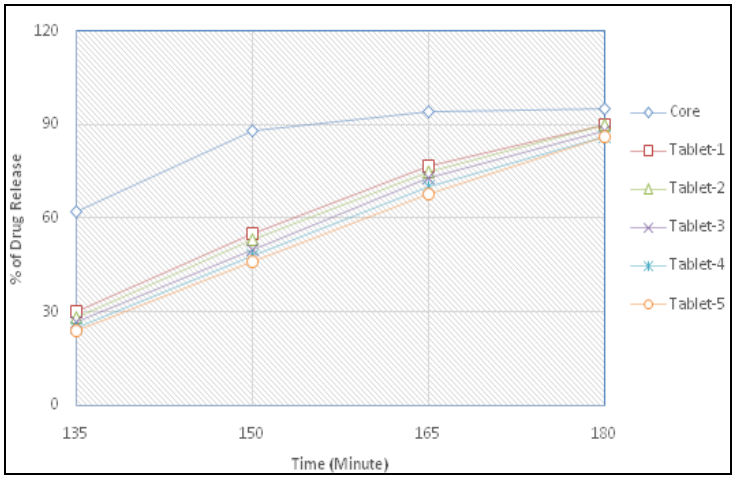

FIG.3: PERCENTAGE OF DRUG RELEASE FROM DICLOFENAC SODIUM (DS) CORE AND COATED TABLETS IN INTESTINAL FLUID (pH = 7.4)

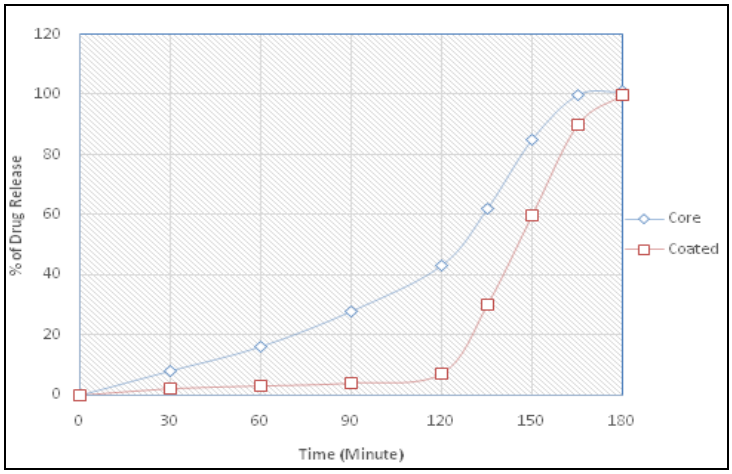

FIG. 4: PERCENTAGE OF DRUG RELEASE FROM DICLOFENAC SODIUM (DS) CORE AND COATED TABLETS (COATED BY PHTHALIC ACID-PROPANE-1,2-DIOL-GLYCEROL CO-POLYESTER) INSTIMULATED GASTRIC FLUID (pH = 1.2) AND IN STIMULATED INTESTINAL FLUID (pH = 7.4)

From the degradation study it was found that phthalic acid-propane-1,2-diol-glycerol co-polyester remained intact in the gastric fluid (pH = 1.2) but gradually degraded in intestinal fluid (pH= 7.4). Enteric coating material resists the release of the drug from the core tablet in the gastric environment but it aids drug release in the intestine. In this study, it was found that the polymer did not degrade or swell in the gastric fluid when coated on a core tablet for as long as two hours.

CONCLUSION: Phthalic acid-propane-1,2-diol-glycerol co-polyester in a biodegradable polymer and it has been tried to apply as an enteric coating material on diclofenac sodium (DS) core tablet. This co-polyester remained intact in gastric fluid (pH = 1.2) but gradually degraded in intestinal fluid (pH = 7.4). So, it might be used as a coating material for drug release system. It has been found that, in gastric fluid the polymer did not degrade till two hours but in intestinal fluid it gradually degrade within 60 minutes. So, phthalic acid-propane-1, 2-diol-glycerol co-polyester has investigated as an enteric coating material on diclofenac sodium (DS) core tablet and results according to B.P. have been obtained. Toxicological test of the co-polyester is yet to be performed.

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