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FORMULATION AND EVALUATION OF MATRIX TABLET OF INDOMETHACIN USING NATURAL POLYSACCHARIDE

Smriti Kumari*, Dharmendra Singh Rajput, Naveen Gupta, Neeraj Sharma

Abstract*:* The present study was carried out to develop matrix tablet for Indomethacin using a combination of Tamarind seed polysaccharide (TSP) and Eudragit S100 as carriers. Matrix tablets containing varying concentration (3 0% - 70 %) of TSP along with 30 % Eudragit S100 were prepared by wet granulation method and subjected to *in vitro* drug release studies. Matrix tablets containing 50 % TSP and 30 % Eudragit S100 (F3 BATCH) was found to release the maximum amount of drug after 24 hour of dissolution study. Drug release achieved from matrix tablets containing a) Guar gum (50%) + Edragit S100 (30%) and b) Guar gum (50%) + Pectin (35%) + Eudragit S100(30%) was little lesser respectively. Though there was statistically significant difference in the amount of drug released from these formulations, a combination of TSP and Eudragit S100 may be considered as a potential candidate for targeting Indomethacin to rheumatic patient.

Key-words: Indomethacin, Matrix Tablet, Eudragit S100, Colon Specific Delivery System, GIT

Introduction*:* Colon-specific medication distribution has been loomed by an amount of approaches abusing fluctuations in the physical limits lengthways the stomach area. The GIT transportation period was used to express colon exact drug distribution schemes which are so intended that their medication announcement is late to the period obligatory for transiting medication after entrance hole to distal share of unimportant intestine i.e., *ileum* and then medication announcement in the colon[1-2]. Issues swaying the shipment period of medicinal amount procedures in the numerous areas of the digestive territory seem to be contingent on food, stomach motility and physical movement of the being, abstained or nourished national of the being. The alteration in pH lengthways the stomach area was too rummage-sale to grow colon specific medication distribution schemes by smearing coverings that remained complete at little pH and melted at unbiased pH[3-4]. The pH of the colon is though; frequently inferior to the pH of the unimportant intestine, which in go may be as tall as 8 or 9, subsequent in an also initial announcement of a medication[5].

An amount of exact local fonts of the colon container be traveled for place exact medication distribution to the colon. In the colon, a wide development of anaerobic micro-organisms is experiential. These colonic micro-floras crop a great amount of hydrolytic as well as reductive enzymes which can possibly be used for colon-specific drug distribution[6]. Pro-drugs and casings founded on azo aromatic polymers and mediums covering azo aromatic cross-links are instances of schemes that are possibly degradable by reductive enzymes free by colonic bacteria[7].

Separately after azo reductase enzyme announcement additional poly-saccharidases similar glucosidases; glycosidases are too free by colonic micro-flora, which are accountable for the squalor of polysaccharides. Henceforth medication distribution schemes based on polysaccharide can too be castoff for colon specific medication distribution[8].

This new distribution device is used to pledge the announcement of the medication in the distal portion of the instinctive. The brawny reductions of the gut partition make weight, which is accountable for crushing and force of the duodenal fillings[9]**.** Pressure-sensitive medication preparations announcement the medication as

*Corresponding author

* **Patel College of Pharmacy, Ratibad-462042, Bhopal, M.P,**

E-mail: smritisinha40@gmail.com,

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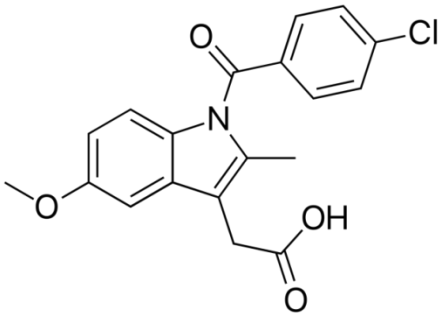
soon as a certain weight boundary is surpassed. Polymers rummage-sale for this theme form firm coatings that are demolished by an upsurge of the luminal weight in the colon produced by peristaltic surfs. Breakdown of a pressure-controlled drug distribution scheme that contains of a gelatin pill with an internal ethyl cellulose covering is activated by peristaltic surfs, abolishing the ethyl cellulose movie[10]. As water entrances into the essential, the low relieved hydroxyl propyl cellulose will start bulge. The cap which is complete of the water-insoluble ethyl cellulose (EC) cannot persist the bulge weight. The ethyl cellulose cap crumbles freeing the lively medication from the ampule inside the capsule. The greatest significant issue for breakdown of the preparation is the width of the water-insoluble ethyl cellulose movie[11].

EXPERIMENTAL

Drug Profile

Indomethacin[12]



Chemistry: 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H- Indole-3-acetic acid

Category: Anti-inflammatory, Analgesic

Description: White to pale yellow, crystalline powder, odourless

Molecular weight: Indomethacin has a molecular weight of 357.79 g/mol

Empirical formula: $C_{19}H_{16}NO_4Cl$

Solubility: Soluble in chloroform; slightly soluble in ethanol (95%) and practically insoluble in water.

Storage: Stored in well closed, light resistant containers

Pharmacodynamics

Mechanism of action: Indomethacin has protuberant anti-inflammatory and analgesic, antipyretic possessions like to persons of the salicylates. Indomethacin is an additional strong inhibitor of the cyclooxygenases than that of aspirin; nonetheless enduring bigotry usually bounds his usage to temporary treating. Indomethacin has analgesic properties distinct from its anti-inflammatory effects, and there is evidence for central and peripheral actions[13].

Pharmacokinetics and metabolism: Oral Indomethacin consumes outstanding bioavailability. Top attentions happen 1 to 2 hours afterward treating. Indomethacin remains 90% certain to plasma proteins and matters. The attentiveness of the medication in the CSF is little; nonetheless its attentiveness in synovial fluid is equivalent to that in plasma inside 5 times of management. Among 10% and 20% of indomethacin is defecated unaffected in the urine, partially by tube-shaped ooze. The mainstream is rehabilitated to sedentary metabolites[14].

Half life: The half-life in plasma is mutable, maybe because of enterohepatic pedaling, but means around 2.5 hours.

Therapeutic usages

- Indomethacin is real aimed at dismissing combined discomfort, bulge, and sensitivity, cumulative grasp forte, and lessening the old-fashioned of morning stiffness.
- It is projected to be about 20 times additional strong than aspirin.
- It overpowers inflammation in a way alike to steroids, nonetheless fewer side properties of calm.
- They are extensively rummage-sale for the action of provocative complaints and sore circumstances such as rheumatoid arthritis, gout, bursitis, painful menstruation, and pain.

Drug Interactions: Indomethacin does not directly modify the effect of warfarin, but platelet inhibition and gastric irritation increase the risk of bleeding; concurrent administration is not recommended. Indomethacin antagonizes the natriuretic and antihypertensive effects of furosemide and thiazide diuretics and blunts the antihypertensive effect of b receptor antagonists, AT1 receptor antagonists, and ACE inhibitors[15].

Adverse Effects: A very high percentage (35% to 50%) of patients receiving usual therapeutic doses of indomethacin experience untoward symptoms, and about 20% must discontinue its use because of the side effects. Most adverse effects are dose-related. Gastrointestinal complaints are common and can be serious. Diarrhea may occur and sometimes is associated with ulcerative lesions of the bowel. Underlying peptic ulcer disease is a contraindication to Indomethacin use. Acute pancreatitis has been reported, as have rare, but potentially fatal, cases of hepatitis[16].

Preformulation studies: Preformulation studies are the first step in development of dosage form of a particular drug substance. It can be defined as investigation of physical and chemical properties of drug substances.

Colour: Weigh accurately a small amount of drug on butter paper and visualize it physically.

Odour: Weigh accurately a small amount of drug on butter paper and observe its odour physically.

Melting Point: The melting point was determined by the capillary method using melting point apparatus. In this method one end of capillary tube was fused by heating it on Bunsen burner. Then capillary tube was filled by pressing the open end gently into meloxicam (pure drug) sample by tapping the bottom of the capillary on a hard surface so that the drug pack down into the bottom of the tube. When the drug was packed into the bottom of the tube, the tube was placed into the slot behind the eye-piece in the melting point apparatus. In other slot of melting point apparatus place a thermometer. Make sure the unit is plugged into the set to zero and then turn it on[17].

Solubility analysis: Solubility may be clear as impulsive communication between two or more substances to form a homogeneous mixture .Qualitative determination of solubility of drug was calculated in different solvent water, methanol, ethanol, 0.1 N HCl, Phosphate buffer (pH 6.8).

METHODS

Isolation of Tamarind Seed Polysaccharide (TSP) [18]

Tamarind seed polysaccharide was ready subsequent approaches by Rao *et al*., in three lots on a workroom gauge. To 20 g of tamarind kernel dust, 200 ml of emotionless purified aquatic was additional and slurry was ready. The slurry was decanted into 800 ml of hot cleansed aquatic. The answer was simmered for 20 notes under rousing disorder in an aquatic immersion. The subsequent reedy strong answer was reserved instant so that greatest of the proteins and fibers established available. The answer was formerly centrifuged at 5000 rpm for 20 minutes. The supernatant was unglued and decanted into double the capacity of absolute ethanol by continuous stirring. The product was pressed between felt. The precipitate was washed with absolute ethanol, diethyl ether and petroleum ether and then dried at 50-60°C under vacuum. The dried material was ground and sieved to obtain granules of different particle size range.

Characterization of TSP by X-ray diffraction[19]: Diffraction pattern of powdered TSP sample was recorded With a Bruker AXS D8 Advance X- ray diffractometer.

Preparation of Indomethacin Matrix Tablets Containing TSP and Eudragit S100 As Carriers

Matrix tablets of Indomethacin were prepared by wet granulation method. Lactose was used as a diluent and a mixture of talc and magnesium stearate was added as lubricant. Tamarind seed polysaccharide (TSP) (50%) and Eudragit S100 (30%) was included in formulations. The composition of the matrix formulations used in the study containing 25 mg of Indomethacin.

TSP was sieved separately and mixed with Indomethacin and lactose. Powders were blended and granulated using 10% starch paste. The wet mass was passed through mesh (10#) and granules were dried at 50°C for 30 minutes. The dried granules were passed through mesh (20#) and these granules were lubricated with mixture of magnesium stearate and talc (2:1). The lubricated granules were compressed using round, flat and plain punches using Rimek mini press -1 machine.

Matrix formulations of Indomethacin with varying concentrations of TSP ranging from 30% to 70% along with Eudragit S 100 (30%) also prepared in different batches in order to identify the formulation with the best release profile.

EVALUATION TEST

Weight variation: Weight variation was calculated as per method descried in Lachman. 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 of tablets differ by more than the percentage listed in table no tablets differ in weight by more than double that percentage**.**

Thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using Vernier caliper.

Hardness: Tablet hardness is measured with hardness testers like Monsanto hardness tester. A tablet is placed in the hardness tester and load required to crush the tablet is measured. The hardness of tablet is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. A good compromise between mechanical strength and disintegration time is achieved for a satisfactory mouth dissolving formulation.

Friability: Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator is used to determine the friability by following procedure. Pre weighed tablets are placed in the friabilator.

Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for at least 4 minutes. At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

% Friability = 1- (loss in weight / Initial weight) X 100

Disintegration Time: Six tablets were placed in each tube of disintegration apparatus. Buffer solution of pH 6.8 was placed in the basket and temperature was maintained at 37°C ± 2°C.pH of the solution was checked by pH meter. The time taken by tablets for complete disintegration was recorded.

***In Vitro* Dissolution Time**

***IN VITRO* Drug Release Studies:** The aptitude of matrix drugs of Indomethcin (containing TSP and Eudragit S100 as carriers) to continue complete in the physical setting of abdominal and minor intestine was measured by imitating entrance to colon transit. Drug announcement educations were approved out by USP XXIII closure device (100 rpm, 37± 0.5°C) in 900 ml 0.1N Hydrochloric acid for 2 hours as the regular stomach draining time is ~2 h. The closure average was substituted with 900 ml pH 7.4 phosphate buffers and verified for 3 hours as the regular small intestinal transportation period is around 3 times. The closure average was then substituted with pH 6.8 phosphate bumper and drug announcement educations were approved out for 24 hours as the normal colonic shipment time is 20-30 hours. 10 ml of example was occupied at the finish of stated period intermissions drinkable and remainder was examined for Indomethacin at 318 nm using UV spectrophotometer. A 10 ml capacity of drinkable, new disbanding average was additional to brand the capacity after each sample removal. Matrix preparations of Indomethacin with varying attentions of TSP ranging from 30 % to 70 % along with Eudragit S100 (30%) were prepared in different batches in order to identify the formulation with the best release profile. Composition of these matrix formulations are given in table 2. The formulation with the best drug release profile identified from the above batch were then compared with the drug release profile of Indomethacin matrix tablets prepared using a) Guar gum(50%)+Eudragit S100 (30%)and b) Guar gum (50%) +Pectin (35%) + Eudragit S100 (30%). Composition of these matrix formulations are shown in table 3 and 4. The above procedure was followed in order to carry out the drug release studies for these formulations.

Wetting Time: A glass Petri dish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was noted as wetting time.

Results and Discussion

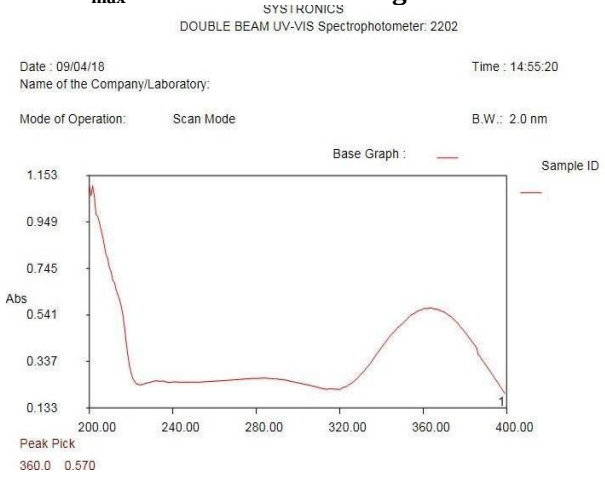
Preformulation Studies of Indomethacin:

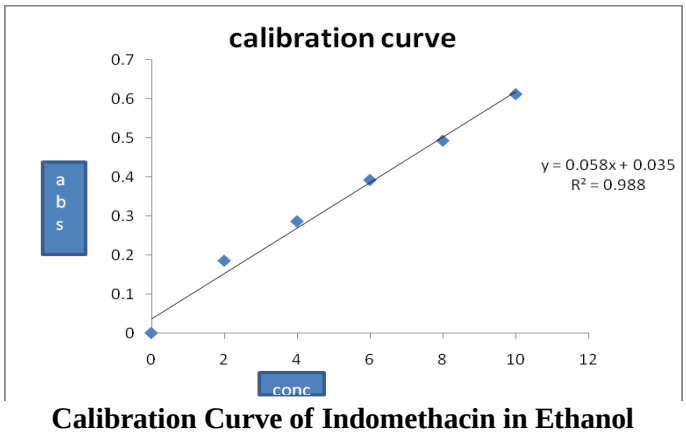
Colour: Indomethacin is off white powder.

Odour: The drug powder was found to be odourless.

Melting point: The melting point of drug Indomethacin was found to be 170°C.

λ_{max} of Indomethacin drug in ethanol





Calibration Curve of Indomethacin in Ethanol

Conclusion: The current studies were approved available to grow matrix tablets for Indomethacin by a mixture of Tamarind seed polysaccharide (TSP) and Eudragit S100 as carriers. Matrix tablets covering variable attentiveness (30%- 70%) of TSP lengthways by 30% Eudragit S100 was ready by wet granulation methods and exposed to *in vitro* drug announcement trainings. Matrix tablets covering 50 % TSP and 30% Eudragit S100 (F3 BATCH) was originate to announcement the all-out quantity of medication afterward 24 hour of closure education. Drug announcement attained after matrix medicines covering a) Guar gum (50%) + Edragit S100 (30%) and b) Guar gum (50%) + Pectin (35%) + Eudragit S 100(30%) was slight smaller correspondingly. However here was statistically important change in the quantity of drug free after these preparations, a mixture of TSP and Eudragit S100 may be careful as a possible applicant for directing Indomethacin to rheumatic enduring.

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