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DEVELOPMENT AND OPTIMIZATION OF INDOMETHACIN COMPRESSION COATED TABLET FOR COLONIC DISEASES

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ABSTRACT

Nature has provided us a wide variety of materials to help improve and sustain of all living things either directly or indirectly. In the view of this, the present investigation was carried out to develop and optimize Indomethacin (IND) compression coated tablet by using Tamarind seed polysaccharide, Xanthum gum, HPMC as a carrier in colon specific drug delivery (CSDD) for the treatment of Inflammatory Bowel Diseases (IBD). The TSP polysaccharide was extract from seeds and it was further characterized for its physical chemical characteristics. The FT-IR and DSC studies were carried out in on order to study the characterization between drug and polymers used. The matrix tablets were prepared by direct compression method with different ratio of the polymers and further evaluated for Post and pre-compression parameters. *In-vitro* release studies were performed in conditions simulating to colon transit. Tablets containing either Tamarind seed polysaccharide or Xanthum gum or HPMC or combinations of them were estimated. Optimized formulations were further evaluated in 2 % rat cecal content. Finally concludes that tamarind seed polysaccharide can be utilized along with the combination of Xanthum gum and HPMC in order to maximize the therapeutic effect on colon where single polymer in coating layer were unsuitable targeting Indomethacin release in colonic region.

INTRODUCTION

The oral route is considered to be most convenient for administration of drugs to patients. After oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and is absorbed from these regions of the GIT depends upon the physiochemical properties of the drug[1.] Oral route of administration always receives more attention in comparison to the other delivery approaches [2]. Oral site specific drug delivery systems to the colon have been gaining interests during the past two decades [3]. Colon specific drug delivery system offers several advantages in the treatment of colonic diseases such as Ulcerative colitis, Chron's disease, irritable bowel syndrome, amoebiasis, colon rectal cancer, but also potential for the delivery of proteins and therapeutic peptides.[4] Various types of pharmaceutical approaches have been used for oral delivery of drugs to the colon which includes time dependent, pH dependent and microbially triggered system which includes prodrug and polysaccharide based system [4, 5]. Among these approaches have disadvantages like pH sensitive system exhibit unpredictable site specificity of drug release because of inter and intra subject variation and almost similar pH values of small

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intestine and colonic fluids [5]. A time dependent system seems difficult for accurate prediction of site for drug release because of wide variation in gastric retention time [6] although the small intestinal transit time (3±1 hr) is relatively constant and less variable [7]. Prodrugs based on azo polymers are specifically reduced by azoreductase enzymes. However, they are expensive and their safety is questionable [8.] Microbially triggered systems are based on compression coating of immediate release tablets with natural polysaccharides which are degraded by anaerobic microflora of the colon [9]. However large amount of coating is required to prevent mature drug release due to higher hydrophilicity of the polysaccharide [10]. Mean while, thicker coating, although minimizes precolonic release, induces sustained release following a reasonable lag time instead of burst release of drug in the absence of specific enzymes or cecal content [11, 12, 13]. Although many polysaccharide like guar gum, pectin, sodium alginate, locust bean gum, chitosan and Xanthum gum have been used as both in compression coating material [14, 15]. Taking the above information, the present investigation was carried out an general and indeed a more rational approach to develop a compression-coated tablet, the coat which should erode slowly enough to prevent or at least to minimize the precolonic release and then to provide an immediate burst release of drugs in the colon irrespective of enzyme metabolism of the polysaccharide by colonic microflora by using Indomethacin (NSAID) as a model drug.

2. MATERIALS AND METHODS

Indomethacin was purchased from Yarrow chemicals Mumbai. Tamarind seed kernel powder were collected from local market, Xanthum gum and HPMC were SD fine chemicals, Mumbai. Natural polysaccharide like Tamarind seed polysaccharide (TSP), Xanthum gum, HPMC were used. TSP obtained from the seed of kernel of Tamarindus indica, posses properties like high viscosity, broad pH tolerance non carcinogenicity, mucoadhesive nature and biocompatibility[16]. TSP is commonly called as Imli and also known as “Indian Date” and obtained from the green tree belonging to family Fabaceae [17].

Fig.1. a) Raw tamarind seeds

b) Tamarind seeds broken

c) TSP powder

ISOLATION OF TSP

The seeds of Tamarindus indica are washed thoroughly with water to remove the adhering materials. Then, the reddish testa of the seeds is removed by heating seeds in sand in the ratio of 1:4 (Seed: Sand). The testa is removed. The seeds are crushed lightly. The crushed seeds of Tamarindus indica are soaked in water separately for 24 h and then boiled for 1 h and kept aside for 2 h for the release of mucilage into water. The soaked seeds are taken and squeezed in a muslin bag to remove marc from the filtrate. Then, equal quantity of acetone is added to precipitate the mucilage. The mucilage is separated. The separated mucilage is dried at temperature 50°C, powdered and passed through sieve number 80.

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The dried mucilage is powdered and stored in airtight container at room temperature .[18, 19, 20]

Characterization of TSP [19,20,21,22]

A) Determination of Purity of TSP: For the detection of purity of gum tests for alkaloids, carbohydrates, flavonoids, steroids, terpins, saponins, tannins and phenols were following test were carried out as per standards and confirmatory tests for extracted polysaccharide also been conducted.

Identifications test for Tamarind seed polysaccharide [19, 22]

A) Melting point determination: the sample of TSP was transferring into a capillary tube and by using Cisco melting point apparatus, Melting point was determined.

B) FTIR: A spectrum is obtained by using FTIR instrument by Potassium Bromide pellet technique.

C) DSC: DSC of TSP is obtained by a differential scanning calorimeter at heating rate of 10^0C/min from 30 to 300^0 C in nitrogen atmosphere 30 ml/min.

3. FORMULATION OF INDOMETHACIN TABLETS [23, 24]

Step I: Preparation of fast disintegrating core tablets: The core tablets were prepared by direct compression method using Composition is tabulated in Table 2. Indomethacin, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and talc were thoroughly mixed using mortar and pestle to ensure complete mixing. Sodium starch glycolate was used as a super disintegrant in the formulation. This mixture was compressed in to tablet single station tablet punching machine using 9.5 mm round, flat faced and plain punches.

Step II: Preparation of Compression coated tablets: The composition of compression coating material is shown in Table 3. All the ingredients are weighed accurately and transferred into mortar and pestle to get uniform mixing. 40% of the total weight (250 mg) of coating mixture was placed in the die cavity in single station punching machine, the core tablet (150 mg) was placed in centre, remaining 60% of coating mixture was added to the die cavity and tablets were compressed using 12.5 mm flat punches. The total weight of the compression coated tablet was about 400 mg.

4. EVALUATION OF TABLETS [25]

The prepared tablets were evaluated for diameter, thickness, hardness, friability. The thickness and diameter of the tablets were measured by using dial thickness apparatus and Vernier calipers respectively. Hardness of the tablet was measured by using Monsanto hardness tester. Both core and compression coated tablets were subjected to friability testing using Roche friabilator. Weight variation study was conducted for prepared formulations as per I.P. standard procedure given in monograph.

A) Disintegration test for core tablets: The test was performed by using Disintegration test apparatus. Six glass tubes that are 3 inches long open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly. To test the disintegration time one tablet was placed in each tube, and the basket rack was positioned in a liter beaker of water at 37^0 C $\pm 0.5^0$C such that the tablets remains 2.5 cm from the bottom of the beaker. A standard motor driver device is used to move the basket assembly up and down through a distance of 5 – 6 cm at a frequency of 28 – 32 cycles per minute.

B) Estimation of Drug content: Tablets from each formulation of compression coated and the core tablets were powder and transfer into 100ml volumetric flask. Firstly, 50 ml of pH 7.4 was taken and allowed to shake in rotary shaker for 24 hrs at 100 RPM and final volume to 100 ml was made with pH 7.4 buffer and filtered with micron filter and filtrate was estimated by using T-20 UV- spectroscopy at 320 nm.

C) Swelling index [26, 27]: Tablets from each formulation are selected, weighed individually (W_1) and placed separately in mesh basket which was placed in 100 ml containing 0.1N HCl for first 2 hrs and latter transferred to pH 7.4 buffers for up to 24 hrs. After 2, 4,6,8,10,12 and 24 hrs the tablets were removed from the basket and excess water was removed by blotting filter paper. The swollen tablets were

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reweighed (W_2) and swelling index was estimated by using formula,

$$SI = (W2 – W1) / W1*100$$

D) Release studies: *In-vitro* release studies [28, 29]: *In-vitro* release studies were performed using USP dissolution test apparatus (basket) type. The dissolution studies were performed in 900 ml dissolution medium, which was stirred at 100 rpm 37±0.5°C, following pH progression method i.e., pH 1.2 for 2 hrs, pH 6.8 and pH 7.4 for rest of studies (24 hrs). Aliquots 5ml of sample with drawn periodically and replaced with fresh medium and aliquots are analyzed by UV-visible spectrophotometer at 228, 273 and 320 nm for pH 1.2, pH 6.8 and pH 7.4 for rest of samples. Each study was conducted in triplicate.

E) Drug release studies in presence of rat cecal contents: Drug release studies are also performed in presences of rat cecal content to examine the effect of microbial degradation on drug release from prepared tablets. The experiment procedure for dissolution studies in presence of rat caecal content was same as described above but with a small changes that 2% rat caecal contents was added to P^H 7.4, simulating colonic fluid.

F) Release kinetics: [30] *In-vitro* release data were fitted into various kinetic models to explain the kinetics of drug release from matrix tablets. The kinetics models used were first order, zero order and Higuchis release. To explore kinetic behaviour, *In-Vitro* release results are fitted into the following Koresmeyer-Peppas equation:

$$M_t / M_\infty = Kt^n$$

Where M_t / M_∞ is the fraction of drug released after time t, K is a kinetic constant and n is release exponent that characterize the drug transport.

G) Stability studies [30,31] : Stability studies was assessed by storing the formulations IF10 at $40^0 \pm 2^0$ at 75^0 C RH for 3 months at the end of every month formulations were evaluated for physical change, drug content, and *in-vitro* release studies**.**

H) Stastical Analysis: The dissolution data collected during experiments are stastically analyzed using Student's t- test. A values of $P<0.05$ was considered stastically significant.

5. RESULTS AND DISCUSSION

The present study was aimed at developing oral colon targeted drug delivery using Indomethacin in treatment of inflammatory Bowel Diseases by utilizing new approach microbially degradable polysaccharide. Combination of core and compressed tablet by utilizing different polysaccharide. Further investigation was carried out to identify most suitable polysaccharide either alone or combination of them. It is a prerequisite for the colon delivery system that it should be remain intact without releasing the loaded drug in stomach but on reaching should completely be depleted of the drug. Hence, attempt was made to formulate compression coated tablet using natural polymer like Tamarind seed polysaccharide, Xanthum gum alone and combination of them. Melting point Determination: the melting point was determined for both Indomethacin and TSP, TSP shows about 160 ^{0} C and pure drug shows about 161.2 ^{0} C. FT- IR studies were carried out for pure drug Indomethacin and polymers used in the preparation of tablets results were recorded in table 1. The observed peaks were matched with peaks given in pharmacopeia which confirms that the supplied sample was Indomethacin. The FT-IR spectra which were obtained in fig 2, it infers that not any presence of additional peaks for new functional groups indicated that no chemical interactions between the drug polymers used in the formulation. Purity of Tamarind seed polysaccharide was determined by various types of phytochemical tests tabulated in Table 4. Which indicates that absences of alkaloids, steroids, flavonoids, saponins, tannins and phenols. Carbohydrates are present which was further confirmed by Molisch test, glucose and Foulger's tests. From Table 5 confirmed that the presence of carbohydrates. Results of all physiochemical properties were obtained within the I.P. limit. Thickness, Diameter, Hardness, Friability and Drug content were estimated and results were tabulated in Table 6. Hardness of the prepared formulation was in the range of 5.84±0.19 to 6.17±0.51 kg/cm^2 indicating that tablets with sufficient hardness could be prepared using the selected polymers. However, in case of Indomethacin core tablets was found to be 3.01±0.19 kg/cm^2.

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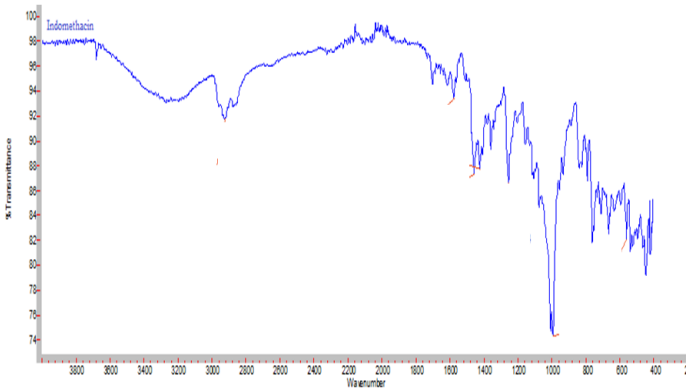

Fig 2 FT-IR spectra of Standard pure drug of Indomethacin

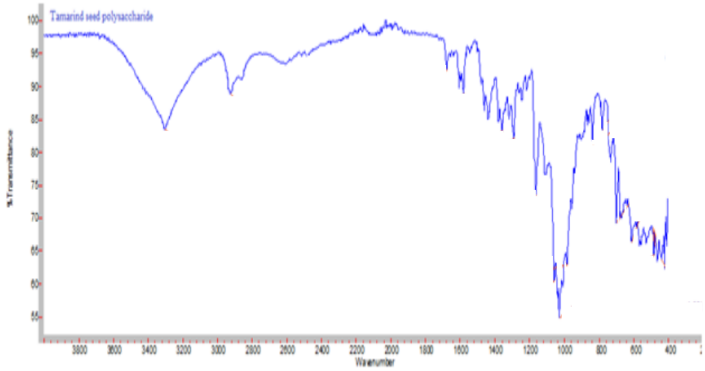

Fig 3 FT-IR spectra of Extracted TSP

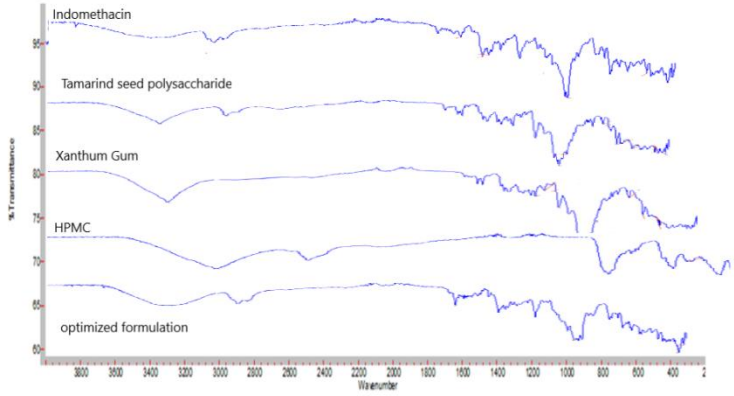

Fig 4 FT-IR spectra of Indomethacin. TSP, XG, HPMC and optimized formulation

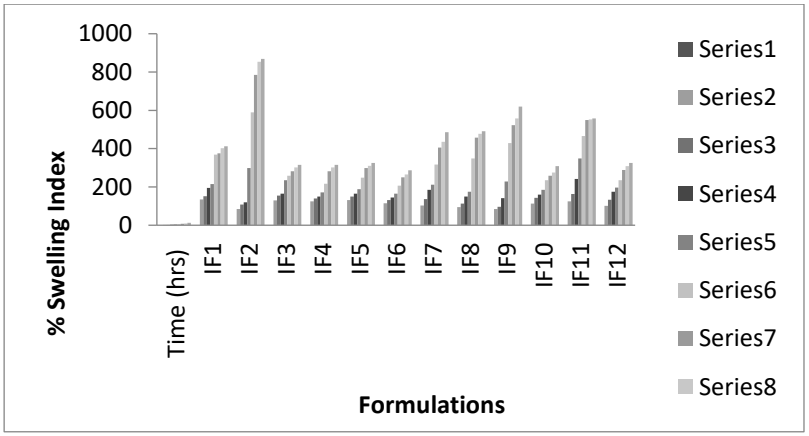

Fig.5. Swelling index of the prepared formulations (IF to IF12)

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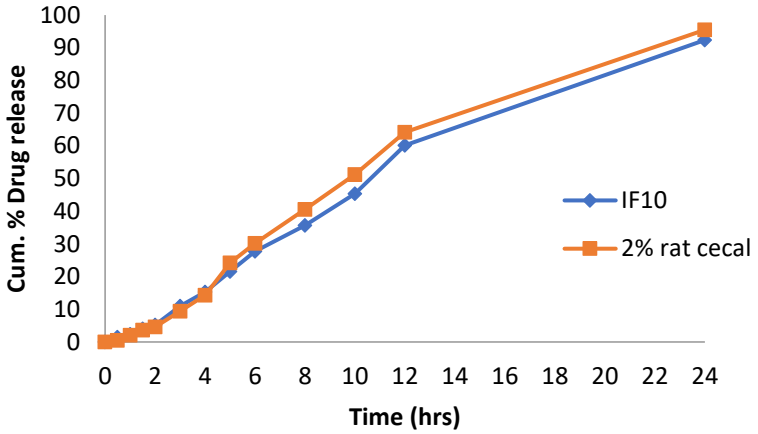

Fig: 6. In-*vitro* release study with and without rat cecal content

Table 1 Interpretation of FT-IR Spectra of Indomethacin

Functional groups	Standard values (cm^{-1})	Observed values (cm^{-1})
C-Cl	750	752.96
COOH out of plane	925	925.81
C-O stretch	1230	1234.06
O-CH_3	1450	1478.79
Aromatic C=C stretch	1600	1691.18
C=O stretch	1715, 1695	1725.15, 1691.02
Aromatic C- H Stretch, -COOH	3400-2500	3400 – 2500

Table 2 Formulation chart core tablet

Sl.No	Ingredients	Quantity (mg)
1	Indomethacin	100
2	Sodium Starch Glycolate	25
3	Microcrystalline cellulose	20
4	Magnesium stearate & Talc	5
	Total weight	150

Table 3 Formulation Chart of Indomethacin Matrix tablets

Formulation	TSP (mg)	Xanthum gum (mg)	HPMC (mg)	MCC(mg)	Magnesium Stearate (mg)	Talc (mg)
IF1	200	-	-	45	3	2
IF2	-	200	-	45	3	2
IF3	-	-	200	45	3	2
IF4	120	-	80	45	3	2
IF5	140	-	60	45	3	2
IF6	160	-	40	45	3	2
IF7	-	120	80	45	3	2
IF8	-	140	60	45	3	2
IF9	-	160	40	45	3	2
IF10	125	25	50	45	3	2
IF11	100	50	50	45	3	2
IF12	75	75	50	45	3	2

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Table 4.Tests for Purity of Gum

Sl.No	Tests	*T. indica*
1.	**Tests for steroids:** Salkowski test, Liebermann- burchard test	-ve
2.	**Tests for triterpenoids**: Salkowski test, Libermann-Burchard test	-ve
3.	**Tests for saponins**: Foam test, Haemolysis test	-ve
4.	**Tests for carbohydrates**: Molisch test, Barfoed's test Benedicts test	**+ve**
5.	**Tests for alkaloids**: Mayer's test, Hager's test, Dragendorff's test	-ve
6.	**Tests for flavonoids(after hydrolysis)** Shinoda test, Zinc/HCL reduction test	-ve

Table 5.Confirmatory tests for extracted polysaccharide

Sr. No.	Test	Observation	Inference
1.	**Molisch Test:** 2ml of sample solution (1%w/v) with 5 drops of Molischs reagent in a test tube. Add gently through the side of test tube, about 2 ml of Conc. Sulphuric acid.	Violet ring at the junction of two liquids was seen	Carbohydrate present
2.	**Solubility:** Sample + Water	Sparingly soluble	Polysaccharide Present.
3.	**C.T. For glucose:** 2 ml of test solution+5%NaoH Solution	Brown precipitate was observed.	Glucose Confirm.
4.	**Foulger's Test:** 3 ml of Foulgers's reagent+1 ml test sol. Boil for 45 seconds and shake well. **Foulger's Reagent:** 40 g of urea in 80 ml of sulphuric acid (40% v/v) then add 2 g of stannous chloride boil until clear solution obtain.	Blue green color was developed	Galactose and xylose confirm

Table 6 Physiochemical Properties of Indomethacin compression coated Tablets

Formulation code	Diameter (mm)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Weight variation (mg)	% Drug content uniformity
Core Tablet	**09.52±.152**	**2.05±0.25**	**3.01±0.19**	**2.84±0.47**	**155.19±0.45**	**99.12±0.37**
IF1	12.53±0.54	2.58±0.19	6.12±0.74	0.88±0.85	395.21±0.32	96.12±0.48
IF2	12.51±0.27	2.57±0.85	6.07±0.19	0.78±0.18	399.12±0.16	97.45±0.47
IF3	12.54±0.19	2.57±0.25	5.98±0.28	0.74±0.36	396.18±0.84	96.12±0.65
IF4	12.58±0.36	2.64±0.17	6.02±0.19	0.89±0.85	400.12±0.45	96.25±0.19
IF5	12.53±0.47	2.59±0.96	5.99±0.31	0.88±0.49	402.13±0.49	95.25±0.52
IF6	12.57±0.85	2.54±0.25	5.87±0.98	0.66±0.74	398.78±0.78	96.56±0.34
IF7	12.59±0.25	2.57±0.19	6.07±0.14	0.78±0.25	402.36±0.28	96.15±0.78
IF8	12.59±0.19	2.59±0.74	6.12±0.25	0.95±0.98	398.12±0.07	96.84±0.25
IF9	12.61±0.63	2.49±0.36	5.84±0.19	0.94±0.15	400.36±0.19	97.85±0.47
IF10	12.53±0.17	2.58±0.95	6.17±0.51	0.78±1.36	402.15±0.25	96.14±0.36
IF11	12.52±0.95	2.51±0.28	5.89±1.09	0.98±1.25	398.12±0.78	99.12±0.75
IF12	12.57±0.34	2.57±0.19	6.15±1.08	0.78±0.15	400.02±0.85	98.12±0.75

The friability of all prepared formulations was in the range of 0.66±0.74 to 0.98±1.25% indicating that the tablets could withstand the mechanical stress during handling. In case of core tablets the percentage of friability was high i.e. about 2.84±0.47%. The disintegration time was measured for core tablet and it was found to disintegrate within 60 seconds. The

faster disintegrate was desired as the core tablet was expected to completely release the drug in the colon region as soon as compression coating was digested by the colonic microbes. Fast disintegration was takes place because of the two reasons, 1) it was a result of sodium starch glycolate rapidly uptake dissolution fluid followed by a rapid and enormous swelling causing faster disintegration of tablets[32, 33] . 2) The hardness of the tablet was very low indicating that the core tablet is loosely compressed. The average weight of the prepared formulation was in the range of 395.21±0.32 to 402.36±0.28 mg whereas in case of core tablets 155.19±0.45 mg. the results of weight variation test indicated that percentage deviation of tablet weights was within acceptable limit as per Indian Pharmacopeia. The drug content was in the range of 96.15±0.78 to 99.12±0.75%. Swelling study was performed for all formulations for duration of 24 hr, in simulating gastric and intestinal fluid shown in Fig 5. For first 2 hrs, swelling study was conducted in 0.1N HCl (pH 1.2) and further in phosphate buffer pH 6.8 and pH 7.4. The swelling behaviour was dependent upon the polymer or their combinations in coating material. In case of the formulations contain Tamarind seed polysaccharide (IF1), Xanthum gum (IF2) and HPMC K15 (IF3) as coating polymers, the swelling index of TSP after 2 hr is 195.16±2.12% which indicates the erosion process is take place in of the tamarind seed polysaccharide (TSP) in first 2 hr & formulation IF2 (Xanthum gum) shows about 120.36±1.98% and Xanthum gum (IF3) shows 165.19±2.16 %, after 8 hr is 384.15±2.08, 785.12 ±1.32 and 275.19 ±1.09% respectively. At the end of 24hr, formulation IF1 (TSP), IF2 (XG) and IF3 (HPMC) shows 559.78±1.08, 985.19±1.36 and 487.12±2.19. IF2 (XG) shows highest swelling and retards effect while compare to TSP and HPMC 24 hrs was 559.78±1.08, 985.19±1.36 and 487.12±2.19. IF2 (XG) shows highest swelling and retards effect while compare to TSP and HPMC. In case of TSP and HPMC the formulation IF4, IF5 and IF6 in pH 1.2 were 150.19 ± 2.18, 165.15 ±2.02 and 145.78 ± 1.98 respectively. In pH 7.4 shows about 281.13±2.15, 298.17±2.47 and 250.54±1.36 at the end of 8 hr , similarly at the nd of 24 hr it shows 350.19 ± 2.45, 345.18 ± 2.69 and 318.19 ± 1.98. From the results of the swelling studies indicates that as TSP proportion in the coating layer increases, the swelling index also increases in SGF, but swelling decreases in SIF.

Xanthum gum and HPMC: The swelling index of the formulation IF7, IF8, IF9 in pH 1.2 shows 185.45±1.115, 150.36±1.28 and 140.89±1.78%, at the end of 8 hr were 404.87±1.10, 458.17±1.08 and 521±1.49 respectively. Similarly at the end of 24 hr formulations showed 512.36±1.09, 558.19±1.45 and 678.12±2.36. results indicates that By increasing Xanthum gum concentration increases swelling index decreases because of retards effect and also presence of HPMC in more concentration , but at the end of 8 and 24 hr they shows increases of swelling effect due to decrease in concentration retards effect was seen and diffusion was takes place.

Combinations of three polymers blend (TSP: XG: HPMC): Swelling index of IF10, IF11, IF12 shows at pH 1.2 for first 2 hrs were 160.19±1.98, 241.36±2.16 and 175.19±2.84, at the end of 8 hr shows 259.19±0.95, 548.78±2.15 and 289.17±1.19 at the end of 24 hr respectively. By results the formulations shows that by the combinations of three polymers retards effect was observed. By increasing the concentration of TSP, Xanthum gum and equal concentration of HPMC will retard the drug effect, swelling and diffusion takes place. Among three formulations IF11 shows more swelling effect when compare to others in all three cases pH1.2 and pH 7.4

***In-vitro* release studies for compressed coated tablets**

1) Effect of Single polymer: formulations with single polymer, the amount of drug released IF1, IF2 and IF3 after 8 hrs were 92.37 (5 hr), 40.12% and 30.19 % respectively. Similarly at the end of 24hrs IF2 and IF3 releases about 55.19% and 38.98%. TSP polymer releases about 50% of drug release within 2 hrs in gastric pH itself whereas as IF2, IF3 were shows slow releasing effect, maximum amount of drug was unable to reach in colonic environment. By this studies it concludes by using single polymer is unable to reach maximum amount of drug in colon.

2) Effect of combinations of two polymers

a) TSP and HPMC: IF4, IF5, IF6

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Among the two polymers, TSP and HPMC Combination shows, 4.56%, 5.52 % and 5.09% of drug release in pH 1.2 at the end of 2 hrs, at the end of 5 hrs in pH 6.8 buffer shows 24.36, 26.97 and 30.14 respectively. In case of pH 7.4 hrs shows 84.32, 80.37 and 76.19% of drug release at the end of 24 hrs. By this release studies indicates that concentration of TSP increases and HPMC decreases indicates that decrease in drug release. Nearly 5% of drug release in Gastric pH, controlled release effect was found in the combination of polymers.

b) Xanthum gum and HPMC: IF7, IF8, IF9

Formulations with a combination of Xanthum gum and HPMC as a coating layer, released 2.51, 3.68, 4.12% in pH 1.2 for first 2 hrs, 15.39, 18.95 and 20.73% in pH 6.8 at the end of 5 hrs respectively, at the end of 24 hrs in colonic pH shows 84.19, 89.25 and 82.36% (Fig.) . results indicates that by combination of polymers shows that formulations containing XG: HPMC indicates by increasing the concentration of Xanthum gum release rate was also increases, by further increasing in the concentrations retard effect more was observed by this indicates Xanthum gum and HPMC combination observed in controlled effect.

c) Effect of Three polymers: IF10, IF11 and IF12 formulation contained HPMC

Dissolution studies were also conducted for formulations with mixture of all three polymers as coating materials to study their influence. HPMC in all the combinations was maintained at 50 mg as the amount was enough to provide the desired release profile for 24 h. The amount of drug released from the formulation F10, F11 and F12 in SGF after 2 h were 5.19%, 4.98±% and 3.06±0.29% respectively, and in pH 6.8 buffers after 8 h were 35.69%, 40.82% and 45.39% respectively. With continuation of dissolution and at the end of 24 hrs in pH 7.4 shows 92.36%, 88.72% and 84.78%. The drug release of formulations IF10, IF11 and IF12 indicated that combination of a three polymer released smaller amount of drug release (> 5%) and Maximum amount release in colonic environment. The release of the drug embedded in a polymeric matrix generally either by erosion of outermost gel layer or dissolution of drug by GI fluid and further diffusion through the gelled polymeric barrier.[34] there is a chances that, the tablets on imbibing dissolution fluid forms gels and the gel like consistency controls the polymeric matrix erosion which leads to faster the drug release.

***In-vitro* release studies in presence of 2% rat cecal contents:**

By considering *in-vitro* release studies data, formulation IF10 was selected to carryout dissolution studies in 2% rat cecal contents. There was difference was found in drug release studies performed in the absence of rat cecal content. The rat caecal content used in the release study was considered to mimic the human colonic environment as it contains microflora which releases many glycosides and degrade the polysaccharides polymers. When the dissolution studies were carried out in the presence of rat caecal content medium, the cumulative percentage drug release from the formulation IF10 after 8 hrs was found to be 35.69% in without rat cecal content, 40.56 % of drug release in presence of rat cecal content which shows in Fig 6. Hence, in presence of rat cecal content, drug release was more from formulations compared to dissolution medium without rat cecal content. This indicates that the drug release from formulations is mainly due to presence of enzymes released by microorganisms of rat cecal content. 2% Rat cecal content was used in the study for the simple reason that the microbial load in the colon is 10^{11} – 10^{12} CFU/ml. From the above two dissolution data (in the presence and in the absence of rat caecal content) significant changes in the release behavior was observed. The results showed that polysaccharides alone neither can be used effectively for targeting the drug to the colon nor for sustaining the release of drug. Hence combination of various polysaccharides for compression coating is ideal for targeting the drug to colon.

Drug Release Kinetics:

The mechanism of drug release was analyzed by plotting drug release data according to Koresmeyer Peppas equation. The ‘n’ value (diffusional exponent) indicates the mechanism of drug release. For a tablet system, the drug release is considered to follow Fickian diffusion if $n<0.45$ while $0.45<n<0.89$, the

drug release is considered to be by anomalous (non-Fickian) transport. 'n' value of 0.89 indicates of zero-order release and n>0.89 indicates a super case-II transport. Analysis of release data according to different kinetic models is shown in table 21. All the prepared formulations followed the first order kinetics. The data from dissolution studies was further fit to Higuchi's equation to analyze drug release mechanism. The r^2 values of Higuchi's plot indicated that the formulation exhibit linearity towards diffusion mechanisms with a correlation values in the range of 0.685- 0.976. Hence to confirm precisely the domination mechanism; the data was plotted according to Koresmeyer-Peppas equation. The 'n' value (diffusional exponent) indicated the mechanism of drug release. For tablet systems, if n <0.45 it suggests the Fickian diffusion; if 0.46 < n < 0.89, it suggests the anomalous (non-Fickian) transport, for n= 0.89, the zero-order release is possible and if n> 0.89, a super case-II transport is operative. In order to predict and correlate the release behaviour of drugs from the tablet, it is necessary to fit them in to kinetics Models. This will facilitate the understanding of mode of drug release such as whether the release is because of only diffusion or only erosion or caused by both diffusion and erosion. The 'n' values were calculated for all formulations. The 'n' values were found in the range of 0.827-1.702, indicating a super case-II transport. These observations confirmed that both diffusion and erosion is dominant mechanism for drug release. Finally concluded that natural polysaccharide like Tamarind seed polysaccharide is ideal for site specificity especially in combination with Xanthum gum and HPMC to target the drug to colon. Among the 12 formulations IF10 (TSP 125 mg: Xanthum gum 25 mg and HPMC 75 mg is ideal for targeting colon. The release rate of Indomethacin from tamarind seed polysaccharide was successfully in target to the colon. It appears that single polysaccharide may not be much suitable for compression coating for specific targeting colon.

Stability test: It was conducted for selected formulation IF10 for a period of 03 months at 40^0 C and 75% relative humidity. The obtained results indicated that there was no much significant change in the designed tablets. The drug content was obtained about 98.5% at the end of 03 months. Release study showed that 92.85% of drug release from the same formulation before storage study where as in Stability study sample showed 91.52 at the end of 03 months, no huge distinction was seen in Indomethacin release from IF10.

6. CONCLUSION:

The present research work has been palatable endeavoured to plan a CTTD of Indomethacin utilizing various polysaccharides like TSP, XG, and HPMC. It is a particular COX-2 inhibitor with pH dependent dissolvability. Preparation was made in to 2 steps, during first step, core tablets are prepared by utilizing sodium starch glycolate as a super disintegrant agent and then further the tablets were compressed with appropriate polymer. All formulations are exposed to physiochemical assessments where they are within limits. The medications discharge from prepared batches indicates that drug release can be modulated to desired release profile by judicious selection of polymer and its amount in formulation. Finally from study concluded that by using single polymer is unable to reach maximum drug in colon (TSP or XG or HPMC) so combination of polymer is best suits for colon targeting where IF10 (TSP: XG: HPMC) is productive for focusing to the colon. Mean while by using natural polymer especially isolated TSP can acts as a drug release retardant, which is evident from the results. The drug release was extended over a certain period of study, suitable treatment for colon diseases like inflammatory bowel diseases.

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