The Pharma Innovation

ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

Received: 01-04-2013
Accepted: 09-05-2013

Vol. 2 No. 4 2013
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

Development and *In-vitro* Evaluation of Colon Targeted Matrix Tablets of Tinidazole

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The present study deals with design of colonic drug delivery with a concept based on a combination of a polysaccharide and a synthetic polymer like, Guar gum, Gellan gum, Xanthan gum, MCC, PVP-K30, and stability study of Tinidazole matrix tablets with Xanthan gum. The matrix tablets were prepared by direct compression method using the PVP-K30 as dry binder (10% of total content), the blend were evaluated for Angle of repose, Carr's index, Bulk density, Tapped density and Hausner ratio. The tablets were also evaluated for Hardness, Weight variation, Friability, Drug content and *in-vitro* release studies in the SGF, SIF and SCF. The evaluation of blend showed good flowability and compressibility. All batches of blend showed drug content in the range of 98 to 99.5% Tinidazole. Hardness, Weight variation and Friability of tablets formulation pass IP specification. From *in-vitro* drug release study it was found that the matrix tablets have zero % release for first two hours in a 0.1N HCL.

Keyword: Matrix Tablets, Xanthan Gum, Tinidazole, Colon Targeting.

1. Introduction

The idea of delaying the transit time of the dosage form through the G.I. tract as a result of prolonging it's gastric residence is due to gastric emptying in humans, which is normally three hours through main absorption area (stomach and upper part of intestine) ,can result in incomplete drug release from the drug delivery system leading to diminished efficacy of the administered dose[1,2].

Formulations that release drug in to the colon rather than the upper intestinal tract are beneficial for a number of clinical situations. Delivery of drugs to the colon via, the oral route is valuable in treating diseases of the colon (Ulcerative colitis, Chron,s diseases, Carcinoma and infections) whereby high local concentration can achieved while minimising side effect that occur because of release higher up in the gastrointestinal tract or because of unnecessary systemic absorption. The colon is rich in lymphoid tissue, up take of antigen in to the mast cell of the colonic mucosa produces rapid local production of antibodies, and this help in efficient vaccine delivery, oral delivery of peptides can also be achieved through colon[3,4,5]. The colon is a friendlier environment for peptides and proteins compared to the upper gastrointestinal tract. Clinically relevant bioavailability may be achieved if the peptide can be protected from acid and enzymes in the stomach and upper intestine[6,7].

1.1 Methods for Targeting Drugs in to the colon:-

Colonic targeting is advantageous in treating diseases of colon, oral delivery of proteins and peptides, where adealy in systemic absorption is therapeutically desirable (nocturnal asthma, arthritis).

1.1.1. Utilizations of Bacterial Enzymes:-

Both prodrugs and dosage forms from which the release of drug is triggered by the action of colonic bacteria enzymes have been devised. Enzymes produced by the colonic bacterial are capable of catalyzing a number of metabolic reactions which includes reduction (of double bonds, nitro group, aldehydes, sulphoxides, kitones, alcoholas, azo groups, N-axides and arsenic acid), hydrolysis (of glycosides, sulphates, amides, esters, nitrates, and sulphonates), deamination, decarboxylation, acetylation, nitrosamine formation, hetrolytic ring fission and estarfication[7,8].

1.1.2. Azo-prodrugs:

Sulfasalazine is a conjugate of sulphapyridine and5-aminosalicylic acid (ASA), with the moleculeslinked by an azo bond (-N=N-). In the treatment of inflammatory bowel dioseases(IBD), sulphasalazine acts **as a 5-ASA prodrug**[3].

1.1.3. Azo-Polymers:

Polystyrene an hydroxyethylmethacrylate crosslinked with divinylazobenzene have been used for colon delivery. Hydrophilic azo polymers containing different ratio of methylmethacrylate and hydroxethylmethacrylate (HEMA) have been synthesized and those with high HEMA content, showed greatest susceptibility to colonic degradation. Similar results have been reported with azo-containing polyamides, azo-containing polyurethane[3].

1.1.4. Disulphide Polymers:

Synthetic ppolymers containing disulphide (-S-S-groups, also reduced in the anaerobicenvironment of the colon, have been reported. One of these polymers is prepared by copolymerization of 3-3'…….bis aminopropyl polytetramethylene oxides and tetraethylene glycol diamine. Glycosidic prodrugs[9].

1.2 Polysaccharides as Matrices/Coating Agent:

The major attraction of most of these materials is that they are already approved for use as pharmaceutical excipients. A mixed coating comprising amylase and ethylcellulose(1:4) has been reported to provide colon specific delivery. Pectin has been evaluated as colon-specificcoating materials. Studies indicated that the degree of metoxylation of pectin and calcium content of the pectin layer influences the solubility of layer and its susceptibility of enzymatic degradation. Pectin has also been mixed with ethylcellulose and used as a tablet coating. Tablet has been prepared from calcium pectate, gaur gum, locust bean gum, treagacanth and xylan. These in combination with methacrylate copolymers (Eudragit) have also been used to coat tablates. A delivery system based on the mucopolysaccnaride, chondroitin, has also been reported. This polymer is found in human colon from sloughed epithelial cells and dietary meat[9,10].

1.3 pH Triggered Delivery System:

The principal group of polymers utilized for the preparation of colon targeted dosage forms has been the eudragits (registered trademark of Rohm pharma, Dramstadt, Germany), more specifically Eudragits L and S. These are anionic polymers which are water impermeable at low pH. Eudragit L100-55 is a copolymer of methacrylic acid and ethyl acrylate which dissolve above pH 5.5. This polymer disperses in water to form latex and thus avoids the use of the organic solvents in the coating process[9,10].

1.4 Time Dependent Deliviery System:

As discussed earlier, although gastric emptying tends to be highly variables, small intestinal transit times are less so (3±1h). So various attempt are made to prevent the release of drug until 3-4 h after leaving the stomach. Osmotic pumps that provide colon specific drug delivery have also been described. The units are

entericcoated and are activated only in the small intestine. A drug-free layer is adjacent to the delivery orifice and this is released over the first 3-4 h following activation.
A delivery system, called the time clock, has been developed comprising a solid core coated with a mixture of hydrophobic material, surfactant and water soluble polymer. The coating is designed to slowly erode away in vitro and in vivo investigation has been reported using tablets coated with a mixture of carnuba wax, bees wax, polyoxyethylene sorbitan monooleate and HPMC[11,12].

2. Material and Method

2.1 Materials

Tinidazole, microcrystaline cellulose, pvp-k30, xanthan gum, talc, magnesium stearate were procured from RKGIT, Gzb.

2.2 Compression of Tablet

Tablets were compressed by direct compression method.

2.3 Evaluation of Blend[13,14,15,16]

2.3.1 Angle of repose (Φ)

The frictional force in a loose powder can be measured by the angle of repose. It is an indicative of the flow properties of the powder. It is given by[11,12,13].

$$\theta = \tan^{-1} h / r$$

2.3.2 Bulk density (D_b)

It is the ratio of the total mass of powder to the bulk volume of powder. It is express in g/mL and is given by[14,15,16].

$$D_b = M / V_0$$

2.3.3 Tapped density (D_t)

It is the ratio of the total mass of powder to the tapped volume of powder. It is express in g/mL and is given by[14,15,16].

$$D_t = M / V_t$$

2.3.4 Carr`s index (I)

It indicates powder flow properties. It is expressed in percentage and given by[17,18].

$$I = \frac{D_t - D_b}{D_t} \times 100$$

2.3.5 Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the fallowing formula[19,20].

$$\text{Hausner ratio} = D_t / D_b$$

3. Evaluation of Blend–See Table - 2

3.1 Evaluation of Tablets[17,18]

3.1.1 Hardness (F_c):

Hardness is the force required to break a tablet in a diametric compression. It was determined using a Pfizer hardness tester. It is expressed in Kg/cm^2[21].

3.1.2 Weight variation:

It is describe that every individual tablet in batch should be uniform weight, a small variation in the weight of the individual tablet to occur. According to Indian pharmacopoeia following percentage deviation in the weight variation is allowed[22].

3.1.3 Friability (F):

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). The % friability was calculated by[22].

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

3.2 Drug Content:

Amount of drug present in a unit dosage form called drug content. It was carried out by non aqous titration using nile-blue as indicator[23].

3.3 Dissolution Studies:

The dissolution test is done for measuring the amount of time required for a given percentage of the drug substances in a tablet to go into solution under specified condition in vitro[22].

3.4 Dissolution Medium:

Dissolution medium used was phosphate buffer of PH 7.4 (volume=900ml)

3.5 Time:
The dissolution of tablet was checked up to 12 hr. for Tinidazole matrix tablets.

3.6 Apparatus Used:
According to IP 2007 apparatus -1 (paddle-shaped) was used.

3.7 Method:
Introduced 900 ml volume of the phosphate buffer of PH 7.4, warm the dissolution medium to between 37±0.5ºC. Allow the tablet to sink to the bottom of the vessel prior to the rotation of the paddle. Operate the apparatus immediately at the speed of 100 rpm. After a suitable time interval, withdraw 5 ml from a zone midway between the surfaces of the dissolution medium; add a volume of dissolution medium equal to the volume of the sample with draw. Filter & measure the absorbance of the filtrate at the maximum at about 310nm.

Dissolution Profile of Formulated Product
4. Result And Discussion
The present study was aimed to use xanthan gum as a carrier for colon spescfic drug delivery using xanthan gum matrix tablets of tinidazole. It was reported earlier that matix tablets of tinidazole containg 40% guhar gum werw potential in targeting colon in the treatment of helminthiasis. Here matrix tablets of tinidazole were prepared by using three different ratio of xanthan gum (Gx_1- 20%,Gx_2- 40%,Gx_3-50%) and tablets was prepared by applying maximum force of compression. The tablets were evaluated for there different parameter and the result were found are as fallows

4.1 Drug Content
Amount of drug present in a unit dosage form called drug content. It was carried out by non-aqous titration using nile-blue as indicator.

4.2 Drug Release Study:
4.2.1 IP method:
The in-vitro release study of the matrix tablets was carried out in IP type I apparatus using 900 ml of 0.1 N HCl as the dissolution medium at 100 rpm and 37 ± 1.0 ^{0}Cfor two hours and 5ml of the samples were withdrawn at every 15 minutes time intervals for up to 2 hours and zero release of drug was found after that dissolution medium was replaced by Sorensen´s phosphate buffer, 900 ml of pH 7.4 for five hour, and 5ml of the samples were withdrawn at time intervals as mention in the dissolution table. 5 ml dissolution medium was replaced after every with drawl and the last sample was withdrawn after 12 hours. The samples were analyzed spectrophotometrically at maximum wavelength 310 nm. Batch Gx_2 shows highest drug release than batch $Gx_1$and Gx_3. The optimum drug release with sustained action was shown by batch Gx_2.

Table 1: Formulation of matrix tablets

S.No.	Ingredient(Mg)	GX_1 20%	GX_2 40%	GX_3 50%
1	Tinidazole	150	150	150
2	Xanthan gum	90	180	225
3	Micro crystalline cellulose	150	60	15
4	Pvp-k30	45	45	45
5	Talc	10	10	10
6	Magnesium stearate	5	5	5

Table 2: Evaluation of Blends

S.No.	Experiment	GX_1	GX_2	GX_3
1	Angle of repose	25.6	28.6	25.2
2	Bulk density	0.351	0.357	0.354
3	Tapped density	O.442	0.446	0.44
4	Carr`s index	19.93	19.95	19.95
5	Hausner ratio	0.794	0.800	0.804

Table 3: Evaluation of Tablets

Evaluation Parameter	Standards Value	GX_1 20%	GX_2 40%	GX_3 50%
Hardness (F_c)	4.0-6.0	3.6 ±0.2	3.5±0.2	3.8±0.2
Weight variation	5%	3.2%	3.1%	3.1%
Friability (F)	NMT 1%	0.56%	0.53%	0.48%
Drug content	98%-101%	98.7	99.6	99.4

Table 4: Dissolution profile of batch GX_1

Time	Conc	Mean	Qt	%Diss
0	0.0000	0.0000	0.00	0.00
5	0.6400	0.6400	576.00	1152.00
15	1.0400	1.0400	939.20	1878.40
30	2.5200	2.5200	2276.40	4552.80
60	3.3300	3.3300	3018.00	6036.00
90	4.3200	4.3200	3925.65	7851.30
150	5.8800	5.8800	5351.25	10702.50
210	7.5600	7.5600	6892.65	13785.30
390	7.6400	7.6400	7002.45	14004.90
570	7.7200	7.7200	7112.65	14225.30
720	7.8200	7.8200	7241.25	14482.50

Table 5: Dissolution profile of batch GX_2:

Time	Conc	Mean	Qt	%Diss
0	0.0000	0.0000	0.00	0.00
5	0.6200	0.6200	558.00	1116.00
15	1.0800	1.0800	975.10	1950.20
30	2.5800	2.5800	2330.50	4661.00
60	3.3800	3.3800	3063.40	6126.80
90	4.4200	4.4200	4016.30	8032.60
150	6.0800	6.0800	5532.40	11064.80
210	7.6000	7.6000	6930.80	13861.60
390	7.7400	7.7400	7094.80	14189.60
570	7.8600	7.8600	7241.50	14483.00
720	7.9400	7.9400	7352.80	14705.60

Table 6: Dissolution profile of batch GX_3

Time	Conc	Mean	Qt	%Diss
0	0.0000	0.0000	0.00	0.00
5	0.5800	0.5800	522.00	1044.00
15	0.9400	0.9400	848.90	1697.80
30	2.5000	2.5000	2257.60	4515.20
60	3.2800	3.2800	2972.10	5944.20
90	4.5400	4.5400	4122.50	8245.00
150	6.0200	6.0200	5477.20	10954.40

210	7.4800	7.4800	6821.30	13642.60
390	7.6600	7.6600	7020.70	14041.40
570	7.7800	7.7800	7167.00	14334.00
720	7.8600	7.8600	7277.90	14555.80

Table 7: Comparative Release Profile:

Time	Conc_1	Conc_2	Conc_3	Mean	SD	RSD(%)
0	0.0000	0.0000	0.0000	0.0000	0.0000	
5	0.6400	0.6200	0.5800	0.6133	0.0306	4.98
15	1.0400	1.0800	0.9400	1.0200	0.0721	7.07
30	2.5200	2.5800	2.5000	2.5333	0.0416	1.64
60	3.3300	3.3800	3.2800	3.3300	0.0500	1.50
90	4.3200	4.4200	4.5400	4.4267	0.1102	2.49
150	5.8800	6.0800	6.0200	5.9933	0.1026	1.71
210	7.5600	7.6000	7.4800	7.5467	0.0611	0.81
390	7.6400	7.7400	7.6600	7.6800	0.0529	0.69
570	7.7200	7.8600	7.7800	7.7867	0.0702	0.90
720	7.8200	7.9400	7.8600	7.8733	0.0611	0.78

Table - 8 Dissolution Data Modeling of Kormeyer – Peppas withF_0Model

Best-fit Values						
Parameter	**No.1**	**No.2**	**No.3**	**Mean**	**SD**	**RSD(%)**
kKP	0.837	0.857	0.832	0.842	0.013	1.573
N	0.359	0.358	0.361	0.359	0.002	0.447
F0	0.000	0.000	0.000	0.000	0.000	

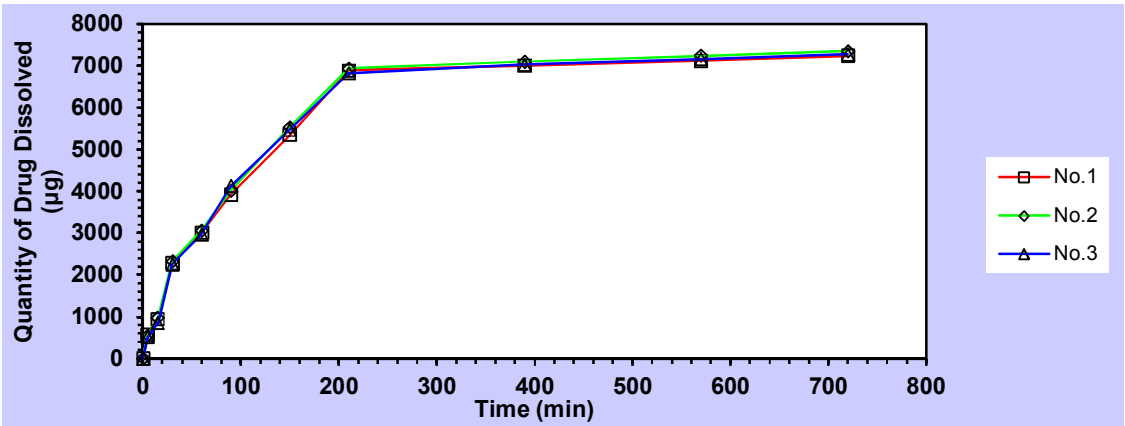

Fig 4: Comparative drug release profile

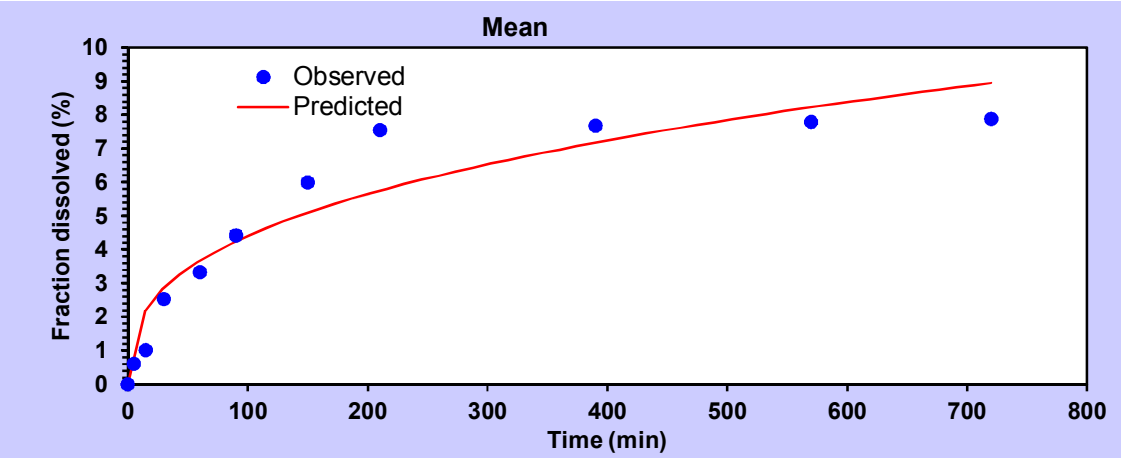

Fig 5: Dissolution Data Modeling of Kormeyer – Peppas withF_0Model

5. Conclusion

The colon targeting matrix tablets of Tinidazole were formulated by taking different ratio of polymer Xanthan gum, Microcrystalinecellulose, Pvp-k30 (as binder) by direct compression method. The formulation batches are best explained by dissolution Data Modeling of Korsmeyer-Peppas with F0 Model.

As we increased the ratio of Xanthan gum polymer the drug content and drug release first increased then decreased and at the same time prolonged the sustained action of the matrix tablets into colonic media. The colonic retention of Tinidazole matrix tablets was best found to be using 40% Xanthan gum. The drug showed zero % release for two hours in 0.1 N HCL indicating that drug would not released in stomach, but in colon. The drug release profile was best observed in using 40% of Xanthan gum polymer and it was 98.37% in 12 hours.

6. Acknowledgement-

I avail this opportunity, with great pleasure and deep sense of gratitude, to express my thanks to my reverent guide Prof. Minakshi Bajpai, College of Pharmaceutical Science (RKGIT, GZB). I am profoundly indebted for her constant inspiration, valuable suggestions, guidance and excellent facilities, with which he led to me to the successful completion of this work. I am extremely thankful to Dr. Bharat Parasher, head department of Pharmacy Manav Bharti University, Solan HP, for his moral support..

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