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An in vitro evaluation of a guar gum matrix formulation targeting colon, using ibuprofen as a model drug

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Abstract

Background: the concentration of a drug in the blood fluctuates over successive administrations of conventional single unit dosage forms. The main reason for this is because conventional dosage forms are designed to release the complete dose of the drug immediately after administration (i.e. burst release effect). These fluctuating drug blood levels can be addressed by means of formulating dosage forms with predetermined drug release profiles.

Specific targeting of drugs to the colon has several therapeutic advantages. Drugs which are destroyed by the stomach acid and/or metabolized by pancreatic enzymes are slightly affected in the colon, and sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis, ulcerative colitis, colorectal cancer and Crohn's disease.

Methods: the matrix tablet of ibuprofen were subjected to in vitro drug release studies in simulated colonic fluids (4% w/v of rat caecal contents) obtained after oral treatment of rats for 7 days of 2% w/v guar gum (1 ml) after completing the dissolution study in 0.1 M HCL (2 h) and pH 7.4 phosphate buffer

Results: Statistically significant differences were observed in drug release profiles from the different polymer combinations. The release kinetics has been found to be governed by the type and content of polymer in the matrix system.

Conclusion: Higher polymeric content of guar gum (70%) decreased the release rate of drug because of the increased tortuosity and decreased porosity.

Key words: drug targeting, matrix tablet, drug release, in vitro dissolution.

Introduction

Various innovative technologies for effective drug delivery have been developed, including implants, nanotechnology, micro-encapsulation, chemical modification and others.

Targeted drug release occurs at or near the intended physiologic site of action or site of absorption. This may have either immediate or extended release characteristics as in nitroglycerine sublingual tablets and transdermal patches, respectively, (Shargel & Yu, 1999)

Purpose: The purpose of the present study is to investigate the effect of guar gum, and or, thanthan gum, and microcrystalline cellulose as a colon specific drug carrier based on the metabolic activity of colonic bacteria, using matrix tablets of ibuprofen as a model formulation.

Colon targeting drugs

Colon-specific drug delivery systems offer several potential therapeutic advantages in a number of colonic diseases such colorectal cancer, Crohn's disease, and spastic colon; it has been shown that local is more effective than systemic delivery. Colonic drug delivery can be achieved by oral or by rectal administration.

Objectives

The main objective of the study is to investigate, whether matrix tablets made of guar gum could be useful in producing colon targeting tablets

Specific objectives

To determine the suitable amount of polymer alone or in combination that could be used to optimize the drug release.

Materials and methods

Materials

Ibuprofen BP

Batch No. YAAA 0398
Manufacturer Dr. Reddy, F, India
Received as a gift from Amipharma laboratories Khartoum-Sudan

Guar Gum

Lot No. 4654
Manufacturer Lucid Colloids Ltd, India
Received as a gift from Amipharma laboratories Khartoum Sudan.

Xanthan Gum

Manufacturer Kong and Wiegand, China
Received as a gift from Amipharma laboratories Khartoum Sudan.

Microcrystalline cellulose (MCC)

JRS pharma-Germany
Received as a gift from Amipharma laboratories Khartoum Sudan

Instruments

Compression machine

Cadmach single punch compression machine, Ahmedabad-8, India

Hardness Tester

Erweka TBH 100, Germany

Friabilator

Erweka TA, Germany

Dissolution Tester

Erweka DT 700, Germany

Spectrophotometer

UV/VIS spectrometer Lambda 2

HPLC

1-Sykam, Isocratic pump model S 1122, auto-sampler Sykam S 5200, with variable wave length programmable UV/VIS detector Sykam S-3200, column nucleosil C18 125mm X 4.6mm ID, particle size 5µm, Kenauer Germany, Auto-sampler Sykam S-5200, software peaksimple.
2-Shimadzu LC/10 AD pd, equipped with auto-sampler, column packed with 5µm reverse phase silica nucleosil C18, Kenauer Germany

Electronic balance

Type A X 120
No. 0432510589
Capacity 120 g
Readability 0.1mg
Shimadzu Philippines Manufacturing INC. (SPM)

Methods

Mixture design technique was utilized to formulate the drug. The independent factors were used at 3 levels, full factorial design. The independent factors are, guar gum, xanthan gum (experimental levels are 10%, 20%, 30% (the first set) and 40%, 50%, 70% in the second set) and microcrystalline cellulose (MCC); a chemo metric filler, was added to the formulation to bring the mixture to the desired amount.

The characteristic of these formulations is that, the amount of matrix forming polymers was decreased gradually for each set of formulations and the reduced amount of matrix forming polymer was replaced by MCC. In all cases the amount of active ingredient was 100 mg.

Table 1. Formulation variables percentages

Formula No.	Guar Gum	Xanthan Gum	MCC
F-1	30%	30%	10%
F-2	30%	10%	30%
F-3	30%	20%	20%
F-4	10%	30%	30%
F-5	10%	10%	50%
F-6	10%	20%	40%
F-7	20%	30%	20%
F-8	20%	10%	40%
F-9	20%	20%	30%
F-19	70%	0	0
F-20	50%	20%	0
F-21	40%	30%	0
F-22	20%	20%	30%
F-23	40%	10%	20%
F-24	20%	50%	0
F-26	50%	0	20%
F-27	20%	0	50%

Preparation of ibuprofen tablets

Matrix tablets of ibuprofen (100mg) containing varying percentage of guar gum, guar and xanthan gum, were prepared by wet granulation method. Microcrystalline cellulose (MCC) was used as a diluent at different concentrations, and magnesium stearate (1%) was used as a lubricant. Ibuprofen, MCC, Guar gum, Xanthan gum, were blended together by dry mixing, and granulated with 10% starch paste. The wet mass was passed through mesh no. 10 and the granules were dried at 45º C for four hours. The dried granules were passed through mesh no. 12, and lubricated with magnesium stearate (1.0%). The lubricated granules were compressed with a single station-tableting machine using 10 mm flat punch. Compressed tablets were tested for their hardness. Tablets friability was determined using the friabilator. Drug content and drug release characteristics were determined using the dissolution tester USP 30.

In-vitro study

The dissolution tests' relating to colon specific drug delivery systems was carried out using the conventional basket method. Parallel dissolution studies in different buffers were used to characterize the behavior of formulations at different pH levels. The matrix tablets of Ibuprofen was subjected for

in-vitro drug release studies in the presence of 0.1 M HCL (2h), pH 7.4 phosphate Buffer (4h) and in simulated colonic fluid (pH 6.8 phosphate buffered saline containing animal caecum contents 4% w/v, obtained after 7 days of enzyme induction with 1ml of 2% w/v guar gum dispersion) (2 hr)

Measurement of drug release

A 5ml aliquot of dissolution medium was withdrawn by a pipette, and filtered by 0.45 μ m. The withdrawn quantity was replaced by the same volume from the stock solution of the media.

Release rates of ibuprofen from the matrix tablet were calculated from the absorbance data in the different pH media at 221 nm.

Drug Release Studies Using a Rat Caecal

The susceptibility of guar gum matrix tablets of ibuprofen to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in 100 ml of simulated colonic fluids after completing the first six hours of study in both 0.1 M HCL (900ml, 2h) and pH 7.4 phosphate buffer (900ml, 4h) (Krishnaiah *et al*, 2001). The drug release study was carried out in a dissolution rate test apparatus (USP apparatus 1, 100 rpm, and 37° C), Erweka DT 700 with slight modification. A beaker (capacity 150-ml) containing 100ml of dissolution medium was immersed in the water contained in the 1000-ml vessel, which was in turn immersed in the water bath of the apparatus. The tablets were placed in the basket of the apparatus and immersed in the dissolution medium containing rat caecal contents. The amount of drug in the different dissolution media was monitored each hour for eight hours, using Perkin Elmer spectrophotometer at wavelength 221.

Mean dissolution time (MDT) value has been used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. A high value of MDT indicates higher drug retarding ability of the polymer and vice versa. The MDT value was also found to be a function of polymer loading, polymer nature and physiochemical properties of the drug molecule.

Results

Tablet hardness

The different formulations were manufactured using (Cademach, Ahemedabad-8-India) single punch machine at the same manufacturing operation conditions, i.e., the same punch, and the same optimum compression force. Tablet hardness was recorded using Erweka TBH 100, hardness tester.

The invented formulations have been screened on the bases of their hardness, friability, and in vitro dissolution release data. Most of developed formulations have shown good results, of hardness, ranging from 50 – 140 Newtons per square centimeter. Formulation of guar gum alone has shown the least hardness, while formulations containing microcrystalline cellulose have shown a higher hardness values. Increasing the amount of microcrystalline in the formulation increased the tablet hardness

Table 2. Effect of Microcrystalline cellulose on tablet hardness

Tablet No.	F 26 (MCC 20%) hardness In Newtons	F27 (MCC 50%) hardness In Newtons
1	63..2	120
2	75	130
3	73	140
4	79.2	115
5	76.2	112
6	76.2	116
7	82	111
8	70.5	108

9	75.2	105
10	60.5	105
Mean	73.1	116.2*
SD	6.7264	11.23289
SE	2.12707	3.55215

* Highly significant $p < 0.001$

From the table it was seen that decreasing the amount of guar gum in F26 (guar gum 50%, microcrystalline cellulose 20%) and substituting it by microcrystalline cellulose in F27 (guar gum 20%, Microcrystalline cellulose 50%) increased the tablet hardness significantly. Therefore the amount of microcrystalline cellulose in the tablet formulation is directly proportional to its hardness.

In vitro drug release study

The formulated matrix tablets that contain varying percentages of guar gum alone or in combination with xanthan gum, or microcrystalline cellulose were studied for their release pattern.

In general and compared to conventional immediate release tablets, all formulations tested exhibited a controlled release pattern of ibuprofen with varying cumulative percentage. Moreover, tablets subjected to in vitro drug
release within all formulations remained swollen till the end of the dissolution test. Incorporation of xanthan gum and microcrystalline cellulose were found to enhance Ibuprofen release, however, increasing the percentage of guar gum was found to retard the drug release.

Table 3. Cumulative percentage release of ibuprofen in 0.1 N HCL (2hr)

time in hr	F1	F2	F3	F4	F5	F6	F7	F8	F9	F 19	F 20	F 21	F 22	F 23	F 24	F26	F 27
1.0	4	3	3	7	5	7	4	2	5	0	0	0	10	4	6	3	7
2.0	8	6	7	12	10	10	7	6	11	0	0	0	13	8	10	5	8

Table 4. Cumulative percentage release of ibuprofen in a phosphate buffer pH 7.4 (4 hr)

time in hr	F1	F2	F3	F4	F5	F6	F7	F8	F9	F 19	F 20	F 21	F 22	F 23	F 24	F26	F 27
1.0	32	26	27	74	70	72	58	49	47	2	10	18	46	15	56	7	56
2.0	34	30	30	76	72	73	60	50	48	5	11	20	47	18	58	8	58
3.0	34	30	30	76	73	74	60	53	51	8	13	21	50	19	58	9	60
4.0	36	32	32	76	73	74	61	53	51	10	15	23	50	21	59	12	60

Table 5.Cumulative percentage release of ibuprofen in phosphate buffer pH 6.8 (2 hr)

time in hr	F1	F2	F3	F4	F5	F6	F7	F8	F9	F 19	F 20	F 21	F 22	F 23	F 24	F26	F 27
1.0	7	5	5	2	4	3	3	8	12	3	4	4	10	8	2	7	4
2.0	12	9	10	3	6	6	5	15	17	7	8	11	17	14	5	13	5

Table 6. Mean dissolution time (MDT) in pH 7.4 (4 Hours)

No	F1	F2	F3	F4	F5	F6	F7	F8	F9	F 19	F 20	F 21	F 22	F 23	F 24	F 26	F 27
MDT	50	53	51	43	49	47	49	50	49	59	51	51	49	52	48	56	49

The results generated in this study showed that the profile and kinetics of drug release were function of polymer level (percentage), and other additives in the formulation.

It is clear from the in vitro study that the amount of drug released is inversely proportional to the guar percentage. Xanthan and MCC have increased the amount of drug release by increasing the erosion rate of the polymer.

The calculated MDT values have shown higher values, which indicate the ability of the polymer to retard drug release. The largest value was obtained for F19 (guar 70%), followed by F26 (guar 50%). These results are in agreement with cumulative percentage release.

Effect of different variables on drug dissolution

Numerous formulations variables are known to affect drug release from hydrophilic tablet matrices. Viscosity grade of polymer, amount of polymer, drug polymer ratio and nature of the drug used in the tablet system (Alderman 1984, Ford *et al* 1985, Hogan 1989) as have been seen from tabulated results tablet hardness was not correlated with the amount of drug released.

Table 7. Effect of drug/polymer ratio on drug release

Formula No.	F19	F26	F27
Drug / Guar	100 / 233	100 / 165	100 / 66
Cumulative percentage release at pH 7.4(4 hours)	10	12	60
Mean hardness	65.2 N	73.2 N	116.2 N

Polymer type

In this study different types of polymer were used in the matrix tablet, at varying percentage for guar gum alone, and different combination percentage of guar gum plus xanthan gum and guar gum plus microcrystalline cellulose, they were chosen to control the drug release and absorption from the tablet system. The study revealed that increasing guar percentage retarded the release of the drug, while increasing xanthan and / or microcrystalline cellulose increased the percent of released drug.

Amount of polymer

Percentage of guar gum in the matrix tablet had a notable effect on drug release and. It is shown that, decreasing the amount of guar gum in F19 by 20% and substituting it by microcrystalline cellulose F26, has increased the amount of drug released in the buffer (pH 7.4) from 10% to 12%. Further decrease in gum by 50% and substituting it by microcrystalline cellulose in F27 has increased the cumulative percentage release to 60%.

Proportion of model drug to the polymer

From table 7, increasing the drug/ polymer ratio from 100/ 233 in F19 to 100/ 165 in F26 to 100/ 66 in F27 has increased the cumulative percentage release of the drug from 10% to 12% to 60%

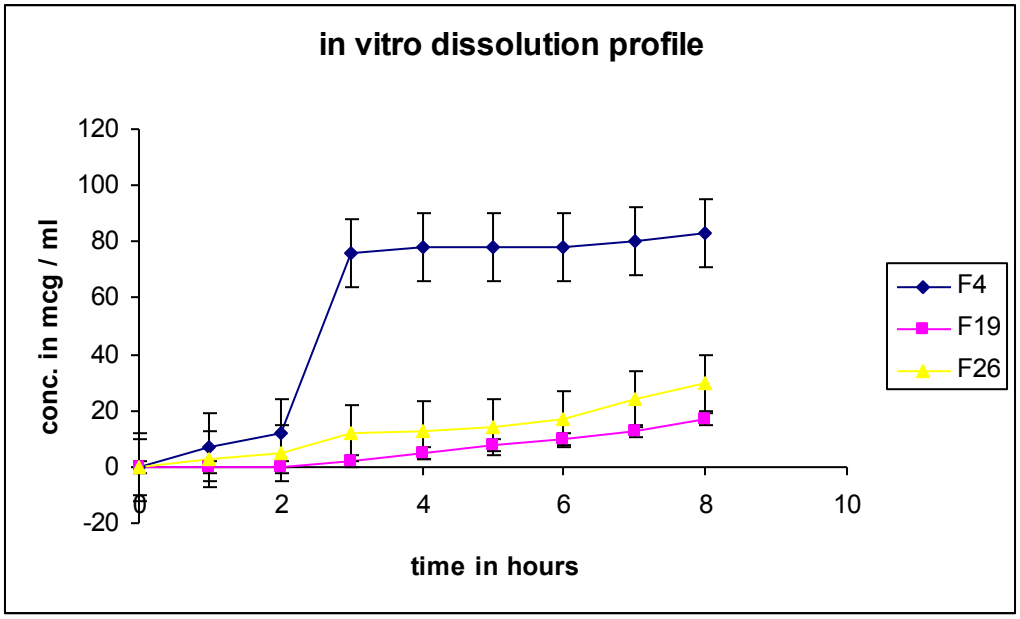

Fig. 1. In vitro dissolution profile of formulations F4, F19, F26

Conclusion

The present study was carried out to develop colon-targeted delivery system for ibuprofen using guar gum as a carrier. Guar matrix tablet containing various proportions of guar gum were prepared and subjected to in vitro drug release studies. Ibuprofen matrix tablet containing < 50% are not suitable for colon targeting as they release most of the drug at early stage. Xanthan gum and MCC were found to modify the release pattern, by increasing the rate and extent of drug release. The ibuprofen matrix tablet containing 70% guar gum has shown the highest MDT values.

1-The results generated in this study showed that the profile and kinetics of drug release were functions of polymer level and drug polymer ratio, and other additives or excipients incorporated in the formulation. A controlled plasma level profile of drug can be obtained by judicious combination of polymers and modulation of polymer content in the matrix system.

2- The compression force and tablet hardness were found not to affect the amount of drug release from guar gum

3- Guar gum was found to have poor compressibility, so increasing the amount of guar gum was associated with low compressibility, and less hard tablets

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