FORMULATION AND DEVELOPMENT OF COMPRESSION COATED COLON TARGETED TABLETS OF BUDESONIDE

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Abstract

Aim of the proposed research was the formulation and evaluation of a compressed coated colon targeted tablet using Budesonide to be used for Crohn's disease. For this purpose, different polymers like Eudragit L 100, Eudragit S 100, and Ethyl cellulose were used to prevent the contact of core tablet containing Budesonide with 0.1N HCl for 2 hours and in phosphate buffer pH 6.8 for 1 hour. Compression coating of core tablet was done by the powder mixture of polymers with different ratios and different amounts of coating mass and it was concluded that the outer coating for each batch was not stable for 2 hours in 0.1N HCl. Hence, it was decided to prepare the granules of the coating polymer mixture. Different batches were prepared by taking three variables and varying their ratios at three levels (low, medium, high) by using Box Behnken Design. Two batches F10 and F14 were selected as optimized batches as they showed evaluation parameters like hardness, friability, weight variation, disintegration test in 0.1N HCl and in phosphate buffer of pH 6.8 within the standard limits in comparison to other batches. These batches also represented acceptable results for all evaluation tests of tablets and their individual dissolution profiles indicated their suitability to be used as colon targeted drug delivery systems.

Keywords: Budesonide, Targeted drug delivery, Eudragit L 100, Eudragit S 100, Ethyl Cellulose, Crohn's disease, Compression coating.

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INTRODUCTION

Colon targeted drug delivery system

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons;

(i) Less diversity, and intensity of digestive enzymes,

(ii) Comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum jejunum, eventually releases the drug into ileum or colon which leads to greater systemic bioavailability.

Why colon targeted drug delivery needed?

The following reasons explain need of colon drug targeting

1. Targeted drug delivery to the colon would ensure direct treatment at the disease site,
2. Lower dosing and fewer systemic side effects.
3. Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
4. Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.
5. The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).
6. Formulations for colonic delivery are also suitable for delivery of drugs which are polar and susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

Opportunities in colon targeted drug delivery

1. In the area of targeted delivery, the colonic region of the GI tract is the one that has Been embraced by scientists and is being extensively investigated over the past two decades.
2. Targeted delivery to the colon is being explored not only for local colonic pathologies, thus avoiding systemic effects of drugs or inconvenient and painful trans colonic administration of drugs, but also for systemic delivery of drugs like proteins and peptides, which are otherwise degraded and poorly absorbed in the stomach and small intestine but may be better absorbed from the more benign environment of the colon.
3. This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis. Moreover, there is an urgent need for delivery of drugs to the colon that reported to be absorbable in the colon, such as steroids, which would increase efficiency and enable reduction of the required effective dose.
4. The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), colitis, Crohn's disease and other colon diseases, where it is necessary to attain a high concentration of the active agent, may be efficiently achieved by colon-specific delivery.
5. The development of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very low because of instability in the GI tract is one of the greatest challenges for oral peptide delivery.
6. The bioavailability of protein drugs delivered at the colon site needs to be addressed.
7. More research is focused on the specificity of drug uptake at the colon site is necessary. Such studies would significant in advancing the cause of colon targeted drug delivery in future.

Mucoadhesive drug delivery system

Adhesion can be defined as the bond produced by contact between a pressure - sensitive adhesive and a surface or the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both. The buccal mucosa lines the inner cheek, and buccal formulations are placed in the mouth between the upper gingivae (gums) and cheek to treat local and systemic conditions. The buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules. The oral

cavity has been used as a site for local and systemic drug delivery.

Compression coating

Compression-coating presents an attractive alternative to spray-coating techniques for high molecular weight polymers. Thick coatings can be applied rapidly and it is a solvent-free coating process. Various materials have been investigated as compression coatings, hydroxypropyl cellulose, polyethylene oxide, micronized ethyl cellulose, Eudragit®

RS, Behenic acid. The chief advantage was the elimination of water or other solvent in the coating procedure. Thus there is no need for a barrier coating to prevent water from penetrating the cores-possibly softening them or initiating an undesired reaction. Such barriers, if efficient. Slow down disintegration and dissolution. The dry coating is applied in a single step (in contrast to the repeated applications of different syrups), reducing the time required to evaporate the water and eliminating the necessity of cleaning the coating pan each time it becomes heavily encrusted with dried syrup. With dry coating. Incompatible substances can be separated by placing one of them in the core and the other in the coating. There may be some reactivity at the interface but this should be negligible in the dry state. In addition, if a drug tends to discolour readily or develop a mottled appearance because of oxidation or sunlight, these problems can be minimized by incorporating the drug in the core tablet. Compression-coated tablets function like sugar-coated or film-coated tablets in that the coating may cover a bitter substance. Conceal an unpleasant or mottled appearance, or provide a barrier for a substance irritating to the stomach or one inactivated by gastric juice. The advent of film coating dissipated much of the advantage of dry coating since larger quantities of tablets can be coated in a short time with film-formers dissolved in organic or aqueous solvents. These films dry so rapidly that there is scarcely sufficient time for a reaction to occur. Most recently, the deposition of film out of aqueous solution and suspension has become feasible. Recent advances in coating equipment, such as the side vented pans, have increased the efficiency of the aqueous coating operation to a point where even aspirin tablets may be aqueous coated without significant hydrolysis. This has greatly increased the popularity of film coating over compression coating. Films produce a minimal increase in the size and weight of the core tablets; monograms and other devices on the core remain legible.

Material and Methods:

Preformulation Studies

The preformulation studies were performed with subject to the following points.

Drug Identification

a)Solubility Studies

b) Melting Point Determination

c)λ max determination of drug

d) **Preparation of calibration curves of Budesonide in phosphate buffer pH 7.4, pH 6.8& 0.1N HCl**

e) Identification of drug by ATR- procedure: Drug- Excipient Compatibility study

Formulation Development

Formulation of core tablets by direct compression method

The core tablets were prepared by direct compression method. Micro crystalline cellulose (MCC) was used as direct compressing agent, carbapol was used as a mucoadhesive agent, magnesium stearate was used as a lubricating agent and talc was used as flow promoter. Micro crystalline cellulose carbapol were mixed together after mixing the mixed powder was passed through sieve no. 44. Talc and magnesium stearate was added and then the ingredients were mixed properly in sufficient time (≈20 min.) and the mixed powder blend was compressed in to tablet using 6 mm punches on 8 station rotary tablet compression machine.

Evaluation of Mucoadhesive Strength of core Tablet

Mucoadhesive strength of the tablet was measured on the modified physical balance. The apparatus consist of a modified double beam physical balance in which a glass slide was sticked below the right pan and additional weight, to make the right side weight equal with left side pan. A glass block of 4.5 cm diameter and 2 cm height. This block was kept in beaker filled with buffer media 6.8 pH, which is then placed below right side of the balance. Goat Intestinal mucosa was used as a model membrane and 6.8 pH buffer media is used as moistening fluid. The goat stomach mucosa was obtained from local slaughter house and kept in a Krebs buffer during transportation. The underlying mucous membrane was separated using surgical blade and wash thoroughly with buffer media. It was then tied over the protrusion in the glass block using a thread. The block is then kept in glass beaker. The beaker was filled

with phosphate buffer media up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments. The one side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and mucoadhesive tablet was established. A preload is placed on the slide for 5 min (preload time) to established adhesion bonding between mucoadhesive tablet and goat or rat stomach mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the beaker drop wise from pipette .The addition of water was stopped when mucoadhesive tablet was detached from the mucosa. The weight of water required to detach mucoadhesive tablet from stomach mucosa was noted as mucoadhesive strength in grams.
Force of adhesion = Mucoadhesive strength /100× 9.81

Optimization of Coating layer composition by using different polymer in varying ratios:
Coating layer compositions containing Eudragit L 100 and Eudragit S 100 were used in the following proportions:

Based on literature review (Yehia S.A.), it was decided to use Eudragit L100 and Eudragit S100 as coating material to protect the core of tablet from acidic environment of stomach.

Table No.1 following ratios of Eudragit L100 & Eudragit S100 were used

S.NO	Eudragit L100	Eudragit S100
1.	40	60
2.	50	50
3.	60	40

Methods of compression coating
As the tablet machine available in lab does not have any special tooling for the purpose of compression coating, it was decided to compress coat individual core tablet. Thus using punch-die numbers 9 & 12 core tablets were coated in following manner:

a) For 100 mg coating material -50 mg of each mixture of powders individually was placed in die cavity followed by the core tablet. There after another 50 mg portion of each mixture of powder was placed individually over the core tablet.
Compression of coating material around the core tablet was performed and the coated tablets were evaluated for hardness, friability, disintegration time, dissolution profile in 0.1 N HCl and the observations were recorded.

b) For 200 mg coating material - 100 mg of each mixture of powder individually was placed in die cavity followed by the core tablet. There after another 100 mg portion of each mixture of powder was placed individually over the core tablet.

Compression of coating material around the core tablet was performed and the core tablet was performed and the coated tablets were evaluated for hardness, friability, disintegration time,dissolution profile in 0.1 N HCl and the observations were recorded.

C) For 400 mg coating material - 200 mg of each mixture of powders individually was placed in die cavity followed by the core tablet. There after another 200 mg portion of each mixture of powder was placed individually over the core tablet.

Compression of coating material around the core tablet was performed and the core tablet was performed and the coated tablets were evaluated for hardness, friability, disintegration time, dissolution profile in 0.1 N HCl and the observation were recorded.

Surfaces showed release of air bubbles. This occurred due to the fact that granules used were of same size (#22) & hence the granule bed had large voids for air entrapment. Upon placing the tablets in aqueous solution, the acidic water replaced the entrapped air which was released as bubbles. This phenomenon reduced the strength of coating. According to literature survey, to fill the voids a sufficient quantity of fines must be added to the granular mass. Hence three different ratios of fines and coarse granules were utilized to find the suitable blend. These were as follows:

Table No: 2. Three Ranges OF Fines and Coarsein Granules

Ratio of Fines & Coarse inGranules	Low	Medium	High
Fines : Coarse	40:60	50:50	60:40

Overall three variables were now used for the design of coating formulations using **Box Behnken Design**.

Formula optimization (for coating of the core tablet) using Box Behnken Design

Table: 3. Variables Used in Box Behnken Design

Independent Variables	Levels		
	Low	Medium	High
X1 = % of polymers (Eudragit L100 – EthylCellulose)	40:60	50:50	60:40
X2 = Coating Mass	100	200	400
X3 = Ratio of Fines & Granules in CoatingMass	40:60	50:50	60:40

Table No. 4. Box-Behnken design for coating layer composition.

No. of runs	Pattern			Ratio of Polymers	Weight of Coating Mass	Ratio of Coarse & Fines in Granules
	X1	X2	X3			
1.	0	-	-	1	100	0.66
2.	0	-	+	1	100	1.5
3.	0	+	-	1	400	0.66
4.	0	+	+	1	400	1.5
5.	-	0	-	0.66	200	0.66
6.	-	0	+	0.66	200	1.5
7.	+	0	-	1.5	200	0.66
8.	+	0	+	1.5	200	1.5
9.	-	-	0	0.66	100	1
10.	-	+	0	0.66	400	1
11.	+	-	0	1.5	100	0.66
12.	+	+	0	1.5	400	1
13.	0	0	0	1	200	1
14.	0	0	0	1	200	1
15.	0	0	0	1	200	1

Same procedure was followed for the preparation of the granules of the coating polymers. And same procedure was followed for the compression coating of the core tablets of all 15 batches. As per results the optimized batches were selected from the dummy formulation and the selected batches were further formulated with the drug, replacing the lactose with budesonide.

Table no: 5. Composition of Core Tablets Containing Budesonide:

Ingredients	Quantity
Budesonide	-
Carbopol	8.3 mg
Microcrystalline cellulose	45 mg
Mg. Stearate	1.2%
Talc	1.2%

e) Identification of Drug by FTIR

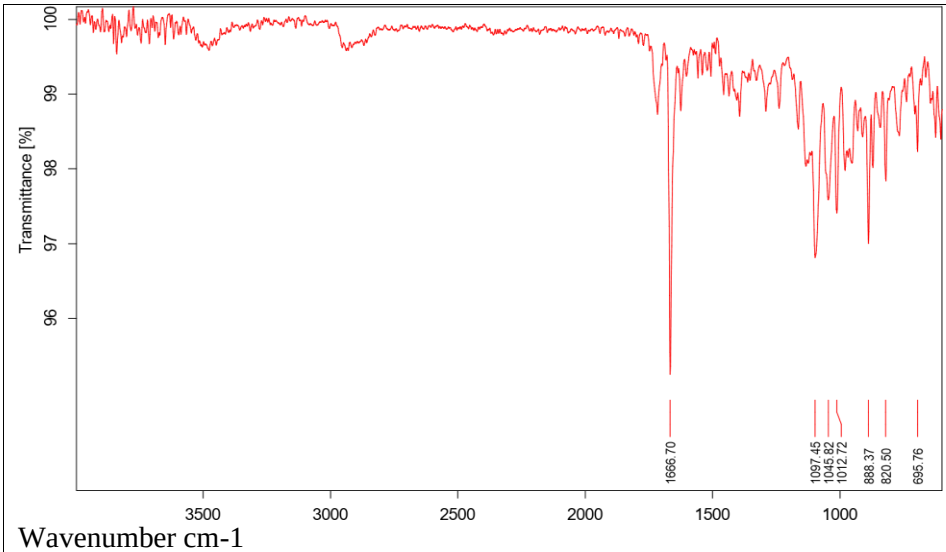
Formulation of Compress Coated Colon Targeted Tablet of Budesonide

From the formulation F10 and F14 were selected as optimized batches. So these two batches were again formulated with drug Budesonide the Box Behnken Design. And the same procedure was repeated for the granulation of the coating polymer and to compress coat the core tablet.

Result & Discussion:

Preformulation study:

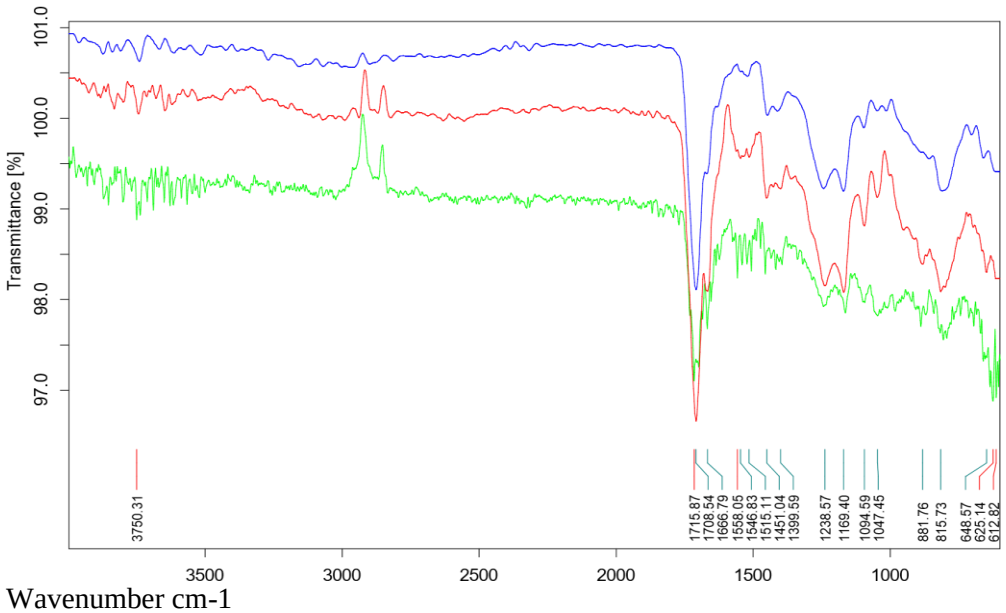
Preformulation study was successfully done. All parameters are within the range.FTIR spectra of drug and drug with physical mixture was as follows.



Wavenumber cm-1

D:\backup\STUDENTS\SAUMYA 2013\BUDESONIDE.0 BUDESONIDE Instrument type and / or accessory	21/02/2013

Page 1/1 **Fig 1** FTIR spectra of budesonide



Wavenumber cm-1

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D:\backup\STUDENTS\SAUMYA 2013\DRUG+ CARBOPOL.0 DRUG+ CARBOPOL Instrument type and / or accessory	19/04/2013
D:\backup\STUDENTS\SAUMYA 2013\DRUG+ MCC+ CARBAPOL.0 DRUG+ MCC+ CARBAPOL Instrument type and / or accessory	19/04/2013

Page 1/1 **Fig 2**FTIR spectra of Budesonide with physical mixture

Evaluation of Mucoadhesive Strength of Core Tablet

S.No	Mucoadhesive strength	Mucoadhesive force (N)
1	0.875	0.0858

Evaluation Parameters for the Prepared coated tablets.

All the batches containing powder polymer ratio (EudragitL100 & EudragitS100), failed in the dissolution study containing 0.1N HCl for 2 hours. On the basis of the above results preparing granules of the polymers was decided.

From the above results, it was observed that all the batches containing granules of polymer ratio (EudragitL100 & EudragitS100), failed in the dissolution study containing 0.1N HCl for 2 hours. In the next batch Eudragit S100 was replaced with Ethyl cellulose.

From the above batches it was concluded that the tablets having coating with the polymer ratio of (EudragitL100 & Ethyl cellulose) showed better integrity in 0.1 N HCl for 2 hours. So, these polymers were selected for the next coating mixtures.

Results of Evaluation Parameters of Tablets Containing Drug:

From the above results, it was observed that all the evaluation parameters of tablets (Batch F10 and F14) were well within the limits and coatings of the tablets of both the batches well tolerated both 0.1 N HCl and phosphate buffer of pH 6.8.

According to the readings and graphs of dissolution profile of both tablet batches (F10 and F14) it was found that maximum percentage drug release was obtained in alkaline pH, i.e7.4.Thus both optimized formulations may be considered suitable as colon targeted drug delivery system.

Different batches were prepared by taking three variables and varying their ratios at three levels (low, medium, high) by using Box Behnken Design. Total 15 batches were formulated as dummy formulation by using lactose in place of Budesonide. From the results of the dummy formulation two batches F10 and F14 were selected as optimized batches because they showed evaluation parameters like hardness, friability, weight variation, and disintegration test in 0.N HCl and in phosphate buffer of pH 6.8 within the standard limits in comparison to other batches. These batches (F10 and F14) were further formulated with Budesonide.

These batches also represented acceptable results for all evaluation tests of tablets and their individual dissolution profiles indicated their suitability to be used as colon targeted drug delivery systems.

Some problems encountered during coating were: the uneven orientation of the core tablet in all tablet batches and inadequate distribution of the coating material at upper surface of tablet. However the later problem was improved by preparing granules of coating mixture.

It is further suggested that the properties of core tablets may be altered to make this formulation a controlled release dosage form. Further changes in polymers used for coating, changes in their proportions, induced changes in granule size distribution etc. may improve coating strength.

Results of Evaluation Parameters of Tablets Containing Drug

Table No.7 Evaluation parameters of tablet

S.No.	Batch	Hardness (kg/cm^2)	Friability (%)	Wt. Variation	Disintegration Time (In 0.1 N HCl For 2 Hours)	Disintegration Time (InPhosphate Buffer pH 6.8 For 1Hours)
1.	**F10**	3.3	0.35	Pass	Crack in the outer coat was observed but inner core of the tablet was not exposed after 2 hours.	The inner core of the tablet was slightly visible through the crack after 1 hour.
2.	**F14**	5.33	0.30	Pass	Crack in the outer coat was observed but inner core of the tablet was not exposed after 2 hours.	The inner core of the tablet was slightly visible through the crack after 1 hour.

Discussion:

From the above results, it was observed that all the evaluation parameters of tablets (Batch F10 and F14) were well within the limits and coatings of the tablets of both the batches well tolerated both 0.1 N HCl and phosphate buffer of pH 6.8.

.In – Vitro Dissolution Study (Batches F 10 and F 14): The in vitro dissolution study was carried out successively in for 0.1 N HCl for 2 hours, then in phosphate buffer of pH 6.8 for next 3 hours followed by phosphate buffer of pH 7.4 for next 21 hours (placed separately in different jars).

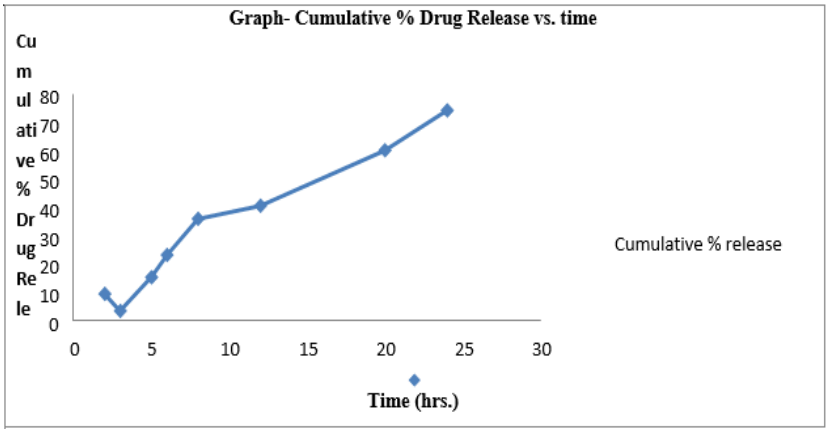

Fig No.3: % Cumulative Drug Release In 0.1N HCl (for 2 hours), Phosphate Buffer 6.8 pH (up to 5 hours), Phosphate Buffer 7.4 pH (up to 24 hours) For F10**.**

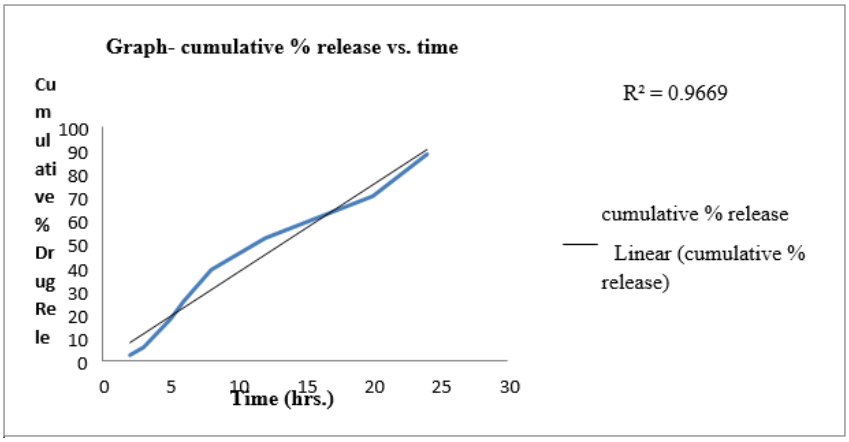

Fig No.4: % Cumulative Drug Release In 0.1N HCl (for 2 hours), Phosphate Buffer 6.8 pH (up to 5 hours), Phosphate Buffer 7.4 pH (up to 24hours) for F 14.

Discussion:

According to the readings and graphs of dissolution profile of both tablet batches (F10 and F14) it was found that maximum percentage drug release was obtained in alkaline pH, i.e7.4.Thus both optimized formulations may be considered suitable as colon targeted drug delivery system

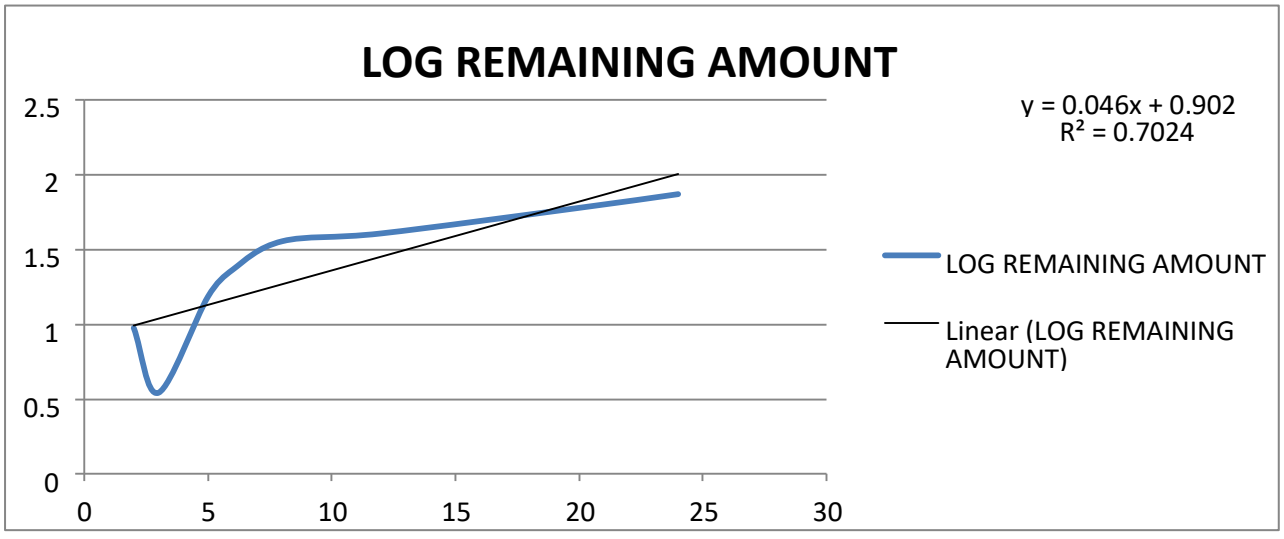

Fig No.5: Log remaining amountFor F10 formulation

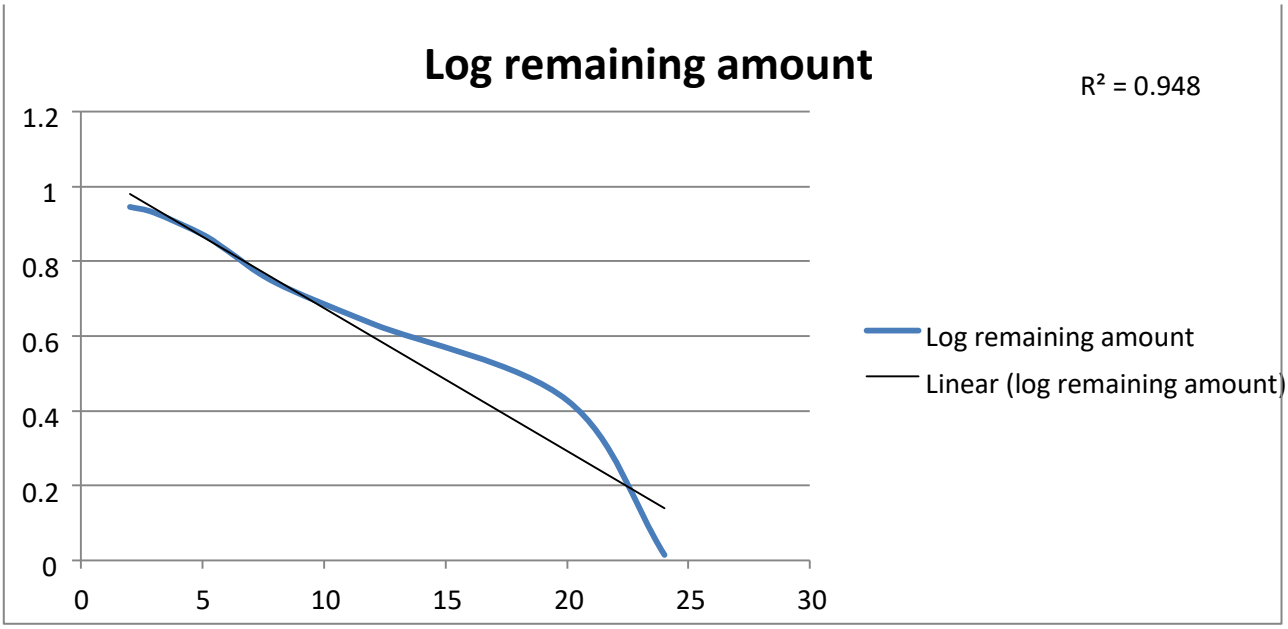

Fig No.6: Logremaining amount for F14 formulation.

CONCLUSION

Aim of the proposed research was the formulation and evaluation of a compress coated colon targeted tablet using Budesonide to be used for Chrohn's disease.

For this purpose, different polymers like Eudragit L 100, Eudragit S 100, and Ethyl cellulose were used to prevent the contact of core tablet containing Budesonide with 0.1N HCl for 2 hours and in phosphate buffer pH 6.8 for 1 hours.

But when the compression coating of core tablet was done by the powder mixture of polymers with different ratios and different amounts of coating mass then it was found that the outer coating for each batch was not stable for 2 hours in 0.1N HCl. In each batch the outer coating of the tablets eroded and the inner core tablets were exposed to the acidic environment. Hence, it was decided to prepare the granules of the coating polymer mixture for coating the core tablet.

Different batches were prepared by taking three variables and varying their ratios at three levels (low, medium, high) by using Box Behnken Design. Total 15 batches were formulated as dummy formulation by using lactose in place of Budesonide. From the results of the dummy formulation two batches F10 and F14 were selected as optimized batches because they showed evaluation parameters like hardness, friability, weight variation, and disintegration test in 0.1N HCl and in phosphate buffer of pH 6.8 within the standard limits in comparison to other batches. These batches (F10 and F14) were further formulated with Budesonide.

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