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ORIGINAL ARTICLE

Formulation and Evaluation of Pulsatile Drug Delivery System for Bisacodyl Tablets

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ABSTRACT
The objective of the present study was to develop and evaluate pulsatile colon specific drug delivery system for bisacodyl tablets. The basic design consist of fast release core tablet using different type of super-disintegrating agent prepared by direct compression method. The tablets were coated with time dependent polymer Eudragit S-100 polymer. The prepared colon specific pulsatile tablets were evaluated for thickness, hardness, weight variation drug content, lag time, in-vitro drug release profile. The lag time of each formulation were observed. The dissolution studies has been carried out pH 6.8 phosphate buffer for time period of 3 hours and then 7.4 phosphate buffer for 10 hours. The temperature of the medium was maintained at ± 0.5ºc. The speed of rotation of basket was kept at 100rpm. Lag time for F1 to F4 showed the range from 415min. to 395 min. and do not show rapid release after lag time. The batch FT4 to FT8 shows lag time between 372min. to 331min. On the basis of evaluation parameters the formulation results of FT8 was selected as an optimized formulation and followed for accelerated stability studies. The rapid disintegration is due to synergistic effect of crosscarmellose and sodium starch glycolate.
Keywords: *Pulksatile, Eudragit S-100, Bisacodyl, Super-disintegrants, Lag time.*

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INTRODUCTION

The versatile approach to develop pulsatile system is to achieve specified lag time period to drug release by using pH dependent polymers. These can be single unit or multiparticulate dosage forms with predictable drug release pattern. This system having advantage to exist in different pH environment at different parts of gastrointestinal tract. So that pH dependent system is targeting at specific site of gastrointestinal tract is possible as well as a desired lag time can be achieve due to dependency of polymer solubility only at particular pH of gastrointestinal tract. pH dependent polymers include copolymers of meth-acrylic acid(various grades of Eudragit), phthalates, carboxy methyl cellulose etc. These polymers are used for enteric coating to protect the drug from degradation in GIT & attain release in specific part of intestine (According to solubility of polymers at specified pH and specific site of intestine.)

The pH of stomach is 2-3(may vary after eating), 6.4-7 in the small intestine and 6.8-8 in the large intestine. pH sensitive polymers those contains carboxy group which make them insoluble at low pH values soluble at higher pH values are used for colon targeting of drug. e.g. Eudragit L (soluble at pH greater than 6), Eudragit S and Eudragit FS (soluble in pH greater than 7) [1].

Advantages

- Due to its ability to release drug in a burst manner, it increases absorption and bioavailability at target site of absorption.
- Limit risk of mucosal irritation.
- Loss of drug by extensive first pass metabolism is prevented.
- Programmed delayed release provides optimal treatment of disease.
- Allow the site specific release of drug (colon specific drug)

Disadvantage

1. Low drug loading capacity and incomplete release of drug.
2. Higher cost of production.
3. Large number of process variables.
4. Lack of manufacturing reproducibility and efficacy [2].

MATERIAL AND METHODS

Materials:

Bisacodyl a generous gift from Syncom formulation Pvt.Ltd, The Lactose, Starch, Purified talc, Magnesium stearate, Eudragit S-100 were purchases from Vishal chemical, Nashik. Sodium starch glycolate, Crosscarmallose sodium, Cross povidone from Highmedia lab pvt.ltd and Acetone from Prasol chemicals Pvt.Ltd

Method:

Pre-compression properties

Angle of repose- was determined by the funnel method. Accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder (2 cm). The powder blends were allowed to flow through the funnel freely onto its surface. The diameter of blend cone was measured and angle of repose was calculated by using following formula the powder cone was measured and angle of repose was calculated by using following formula. [3]

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

Bulk density- powder belnd were transferred into a 50 ml measuring cylinder without tapping during transfer the volume occupied by the powder was measured. It is given by the formula. [4]

$$\text{Bulk density (Db)} = m/v0$$

Tapped density- was achieved by tapping the measuring cylinder which contains the sample for certain tapping's mechanically. During tapping, particles gradually pack more efficiently, the powder volume decreases and the tapped density increases. After observing the initial volume of powder occupied in the 100ml measuring cylinder and then subjected to 50 tap's in the bulk density apparatus. After 50 tapings the final volume is noted down and the results are tabulated.

$$\text{Tapped density (Dt)} = m / Vt$$

Compressibility Index- It is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as Carr's compressibility index. It is indirectly related to the relative flow rate. Carr's compressibility index was determined by the given formula.

$$\text{Compressibility index} = \frac{Vo - Vf}{Vo} \times 100$$

Hausner's ratio- It is very important parameter to be measured since it affects the mass of uniformity of the dose. This usually predicted from Hausner's ratio and angle of repose Measurement Hausner's ratio related to inter-particle friction and, as such could be used to predict the flow properties Table No: shows the flow description and corresponding hausner's ratio. It is determined by the formula.[21]

$$\text{Hausner Ratio} = Vo / Vf$$

Formulation of rapid release core tablet by direct compression

The inner core tablet of bisacodyl was prepared by direct compression method. The ingredients are sieve from sieve no.80. An accurately weighted 5mg of drug bisacodyl and other mixture like bisacodyl, lactose monohydrate, microcrystalline cellulose, cross povidone, sodium starch glycolate, mix in poly bag for 10min. followed by addition of magnesium stearate as lubricating agent. The blend was directly compressed at weight of 86 mg using the 6mm punch on ten- station rotary tablet machine. [4,5]

Table no.1:Formulation chart for bisacodyl core tablet

INGREDIENTS In (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Drug	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1
Lactose Monohydrate	69	66	65	67	69	66	64	62
Microcrsytalline Cellulose	09	11	10	7.5	06	6.5	6.5	7
Cross Povidone	01	02	04	05	-	-	-	-
Sodium Starch Glycolate	-	-	-	-	2.5	04	05	06
Crosscarmallose Sodium	-	-	-	-	02	03	04	04.5
Talc	1.5	1.5	1.5	1	0.5	0.5	0.5	0.5
Magnesium Stearate	0.5	0.5	0.5	0.5	1	1	1	1
Total	86	86	86	86	86	86	86	86

Formulation of coated tablets

The bisacodyl rapid release core tablets were further coated with 12% of Eudragit S-100 to release the drug in colon where the pH around 7 to 7.4. The concentration of coating solution of Eudragit S-100 was prepared in mixture of Isopropyl alcohol (70%) and acetone (30%). The Di-butyl phthalate was in 1.5% was used as plasticizer to make the coating more pliable. The coating of matrix tablet was performed by immersion in the coating solution. [7,8,9]

Table no.2: Parameters used in coating

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
EudralitS-100 (%)	12	12	12	12	12	12	12	12
Di-butyl phthalate(%)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
IPA:Acetone 70:30	100	100	100	100	100	100	100	100
% Weight gain	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Evaluation of core tablet and coating tablet

The tablets were checked for weight variation. Tablet thickness was measuring using screw gauge. Hardness of core tablet was determined using Monsanto hardness tester, friability was determine was using Roche friabilator (EI digital chamber) for core tablet and coated tablet individually.

Uniformity of content was calculated by powdered 20 tablets, Weight accurately a quantity of powder containing about 40mg of bisacodyl. Shake with 70ml of chloroform for 30 minutes and dilute with sufficient amount of chloroform to produce 100ml. Mix well, filtered and diluted 10ml of the filtrate to 100ml. with chloroform. The absorbance was measured at maximum at about 264nm. And the content of bisacodyl was calculated by taking 148 as the specific absorbance at 264nm.[10]

***In-vitro* Dissolution Studies for Coated Tablet**

The dissolution study of bisacodyl coated tablet was carried out using dissolution test apparatus USP-II paddle type. The dissolution medium consisted of 900ml of standard buffer of pH 1.2 for 2 hour. The tablet then, transferred to pH 6.8 phosphate buffer for time period of 3 hours and then 7.4 phosphate buffer for 10 hours. The temperature of the medium was maintained at ± 0.5ºc. The speed of rotation of basket was kept at 100rpm. The Sample was withdrawn after 30min. of time interval. The sample withdrawn was replaced with the fresh dissolution medium equilibrated at the same temperature. The drug release at different time intervals from the dosage form the dosage form is measured by UV visible spectrophotometer, at 264nm.[4-7]

FT-IR Study

The drug–excipient compatibity was conducted by FT-IR study. For FT-IR study the drug, excipients, mixture of drug and excipients, mixture of drug and polymer, and individual polymer were chosen. Then the KBr pellet was placed in sample holder of FT-IR spectrophotometer. The spectra were recorded in the wave number region of 4000-400cm-1. In each case, the spectrum was compared with the pure bisacodyl spectrum to detect the interaction.[11]

Accelerated stability study

As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C±2˚C / 75% RH±5% RH for a period of 3 months. The tablets were packed blister packing material and loaded into the stability chamber under 40±2˚C / 75% ±5% RH and the samples were analyzed at 0, 1, 2and 3 months time points [13].

RESULTS AND DISCUSSION

Table No.3: Micromeritic properties of bisacodyl

API	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility Index (%)	Hausners Ratio
Bisacodyl	0.429	0.524	18.12	1.22

The micromeritic properties of active pharmaceutical ingredient bisacodyl were studied. The bulk density was found to be 0.429g/ml. The tapped density was found to be 0.524g/ml. The compressibility index was found to be 18.12% and the Hausner's ratio was 1.22. The studies complies with the standard references.

FT-IR- Spectrophotometric analysis of bisacodyl

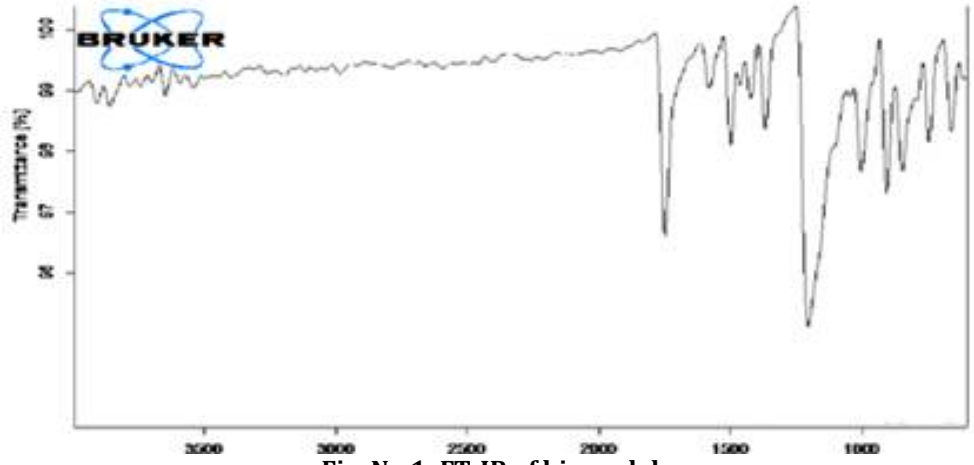

Fig. No.1: FT-IR of bisacodyl

Drug-excipient FT- IR compatibility studies

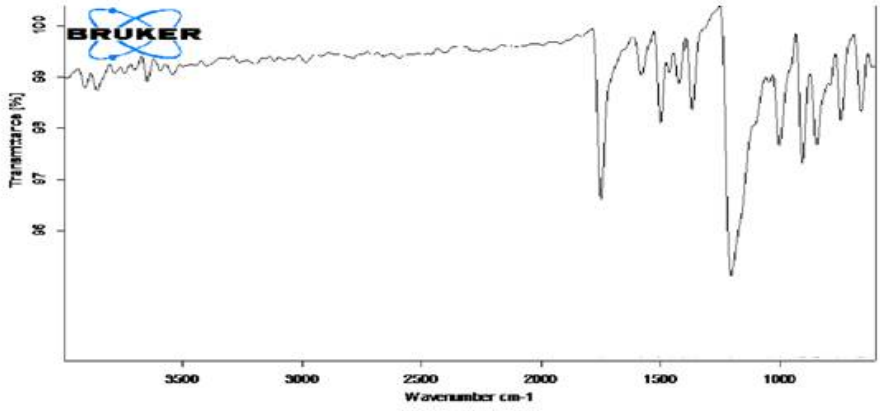

Fig. No.2:FT IR spectra of bisacodyl and excipients.

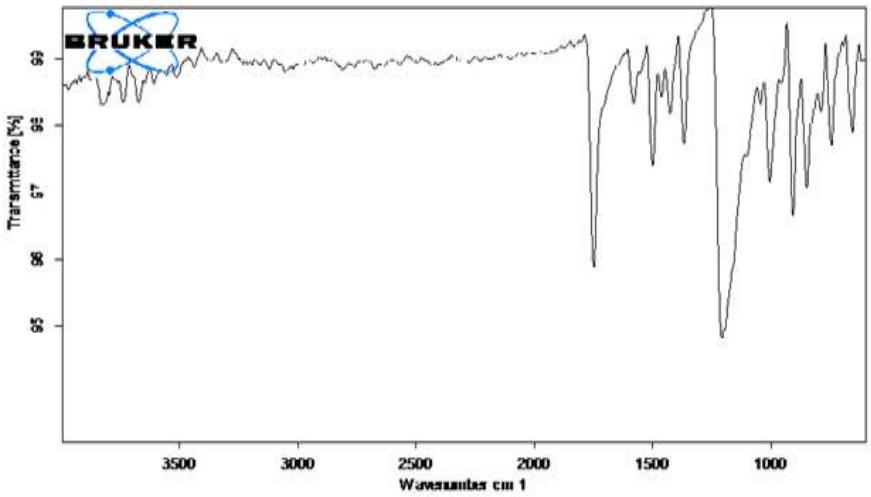

Fig.No.3: FTIR Spectra of drug with eudragit S-100

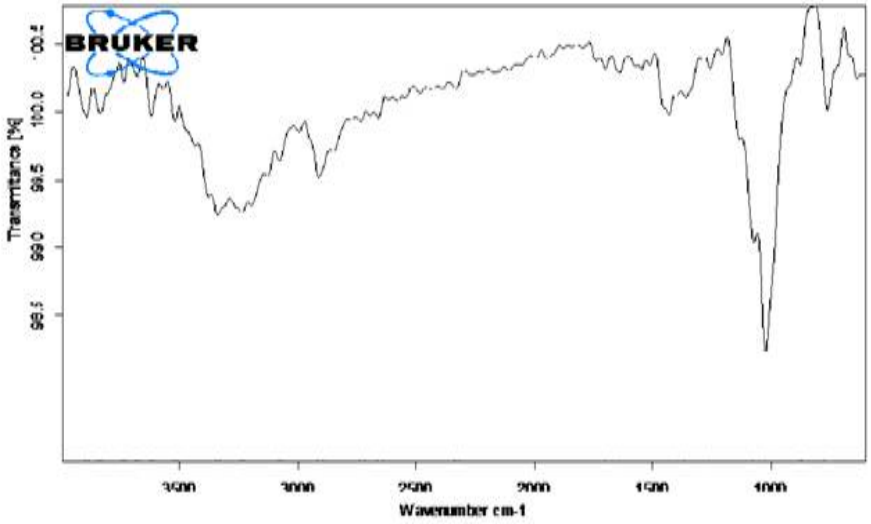

Fig. No.4: FTIR Spectra of coated tablet

The FT-IR studies of pure bisacodyl and polymers with bisacodyl were carried out to study the interaction between the drugs and excipient analyzed. Fig. 1 indicates the FT-IR Spectra of active pharmaceutical ingredient bisacodyl. The characteristics peak due to pure bisacodyl has appeared in spectra without any markable changes in the position. It indicates that there is no any chemical interaction between bisacodyl and polymers. Fig. 2 shows the FT-IR Spectrum of Drug and Excipients, while the Fig. 3 and Fig. 4 are showing FT-IR Spectra for drug with eudragit and coated tablet respectively [20].

EVALUATION OF PRE COMPRESSION PARAMETERS FOR POWDER BLEND

Table No.4: Pre-compression parameters for powder blend

CODE	Angle of Repose	Bulk density* (g/ml)	Tapped density* (g/ml)	Compressibility Index*(%)	Hausners Ratio*
F1	32.64 ±0.64	0.56±0.07	0.65±0.02	13.84±0.65	1.08±0.03
F2	31.54 ±0.12	0.57±0.09	0.66±0.05	13.63±0.10	1.10±0.02
F3	32.32 ±0.28	0.60±0.05	0.69±0.01	13.04±0.22	1.10±0.01
F4	29.17±0.32	0.61±0.07	0.70±0.09	12.85 ±0.015	1.14±0.02
F5	30.99±0.16	0.60±0.03	0.67±0.04	10.44±0.019	1.11±0.03
F6	29.56±0.24	0.61±0.08	0.68±0.03	10.29±0.24	1.11±0.05
F7	29.94±0.39	0.61±0.04	0.69±0.08	11.59±0.54	1.10±0.06
F8	28.67±0.69	0.62±0.01	0.69±0.07	10.14±0.35	1.11±0.04

EVALUATION OF FAST RELEASE CORE TABLET:

Table No.5: Evaluation of fast release core tablet.

CODE	General appearance	Weight variation (mg)	Thickness* (mm)	Friability* (%)	Hardness (kg/cm²)	Disintegration Time # (minutes)	Uniformity Content
F1	Round Convex	86±0.5	2.10±0.05	0.32±0.05	4.61±0.3	4min01sec	99
F2	Round Convex	87±0.4	2.12±0.04	0.35±0.03	4.67±0.2	4min02sec	100
F3	Round Convex	85±0.6	2.07±0.03	0.65±0.06	4.71±0.1	3min08sec	98
F4	Round Convex	86±0.6	2.09±0.1	0.95±0.07	4.73±0.2	3min01sec	99
F5	Round Convex	86±0.7	2.13±0.4	0.15±0.05	5.00±0.3	1min11sec	102
F6	Round Convex	87±0.3	2.06±0.06	0.14±0.08	4.10±0.1	87sec	101
F7	Round Convex	87±0.9	2.11±0.01	0.13±0.07	4.56±0.2	61sec	102
F8	Round Convex	86±0.3	2.08±0.4	0.27±0.07	4.61±0.3	14sec	97

EVALUATION OF COATED TABLET:

Table No.6: Evaluation parameter for coated tablet

CODE	General appearance	Weight variation (mg)	Thickness* (mm)	Friability* (%)	Hardness (kg/cm²)	Uniformity Content
FT1	Round Convex	102±0.6	3.40±0.05	0.86±±0.05	4.65±0.09	98
FT2	Round Convex	105±0.7	3.42±0.04	0.74±0.03	4.90±0.1	97
FT3	Round Convex	104±0.4	3.35±0.03	0.65±0.06	4.98±0.2	97
FT4	Round Convex	107±0.9	3.32±0.1	01±0.07	4.60±0.3	98
FT5	Round Convex	106±0.4	3.50±0.4	0.95±0.05	5.10±2	96
FT6	Round Convex	104±0.4	3.49±0.06	0.89±0.08	4.21±0.3	97
FT7	Round Convex	102±0.9	3.38±0.01	0.52±0.07	4.82±0.5	96
FT8	Round Convex	101±0.9	3.34.±0.07	0.52±0.07	4.75±0.4	98

***In- vitro* dissolution and drug release study for coated tablet:**

Table No.7: Determination of lag time for coated tablet

Batches	Lag time (min)
FT1	415
FT2	408
FT3	401
FT4	395
FT5	372
FT6	368
FT7	345
FT8	331

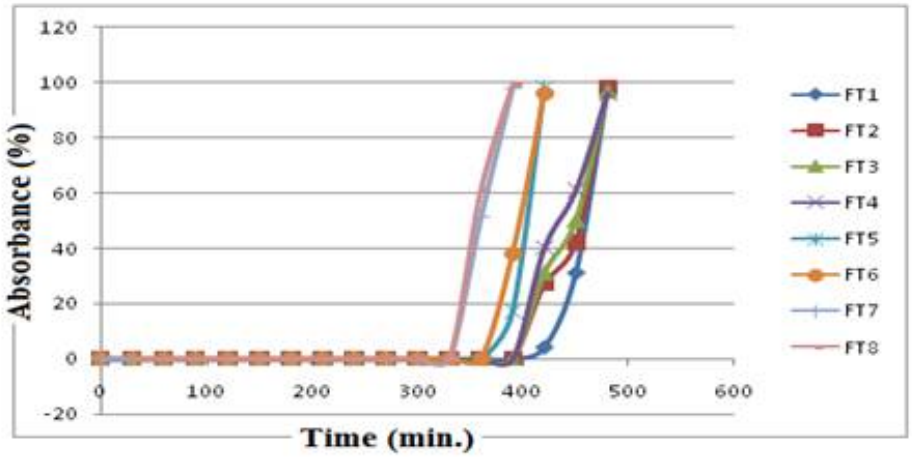

Fig. no.5: % Drug release of Bisacodyl pulsatile tablets

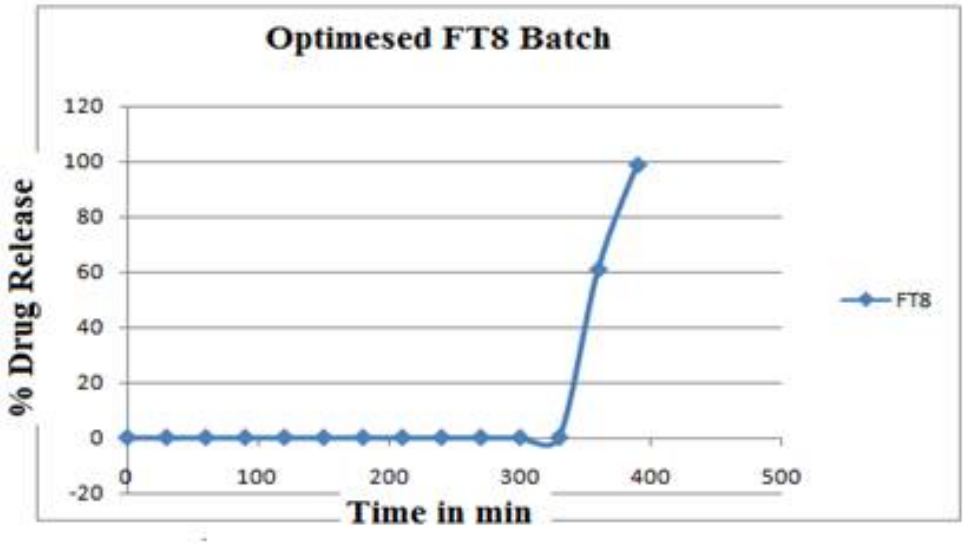

Fig. No.6: % Drug release of Optimed Batch FT8

DISCUSSION

The dissolution profile of all FT8 batches shows decrease in lag time with increase in concentration of sodium starch glycolate and crosscarmellose sodium. Lag time for F1 to F4 showed the range from 415min. to 395 min**.** and do not show rapid release after lag time. The batch FT4 to FT8 shows lag time between 372min. to 331min**.** where, concentration of sodium starch glycolate and crosscarmellose sodium increased gradually as well as batch FT4 to F8 show the rapid drug release after the lag time. The sodium starch glycolate having not only superdisintigrant but also having swelling property it help to rapture the coating layer of Eudragit S-100 and give rapid drug release. The rapid disintegration is due to synergistic effect of crosscarmellose and sodium starch glycolate [20,21].

Accelerated stability data of the formulation (FT8)

Optimized batch FT8 was selected for accelerated stability study.

Table No.8: Accelerated stability data

Physical Parameters	**Storage conditions**			
	40 ºc ±2º c/75% RH±5% RH			
	Initial	**1st month**	**2nd month**	**3rd month**
Physical appearance	White , Round shape tablet	White , Round shape tablet	White , Round shape tablet	White , Round shape tablet
Avg. weight * (mg)	101±0.9	101±0.4	100±0.6	100±0.8
Hardness (kg/cm²)	4.75	4.73	4.72	4.72
Thickness (mm)	3.34.±0.07	3.34.±0.02	3.32.±0.07	3.32.±0.07
Lag time(min)	310	312	315	316
Assay	98	98	97	96

Accelerated stability studies were carried out for the optimized formulation batch (FT8). 20 tablets were packed in blister packing and loaded in the stability chamber for 3 months at 40˚C±2˚C / 75% RH±5% RH. There is no any Significant changes was observed in the physical parameters, drug release and drug content when stored at 40˚C±2˚C / 75% RH±5% RH for 3 months. The assay of tablet found to be 96%. were satisfies the pharmacopeial limits. Hence it is concluded that the formulated coated tablets were stable.

The FT-IR spectra of initial coated tablet compare with FT-IR spectra after 3month. There is no significant changes were observed Hence it is concluded that the formulated coated tablets were stable and there is no interaction of excipient with drug after 3 month [20,21].

CONCLUSION

The bisacodyl pulsatile tablet was prepared successfully by direct compression method. The formulated tablets were evaluated. If the concentration of sodium starch glycolate and crosscarmellose sodium increased simultaneously gradually and show the transit drug release after the lag time. The sodium starch glycolate having not only superdisintegrant but also having swelling property it help to rapture the coating layer of Eudragit S-100 and give rapid drug release. The rapid disintegration is due to synergistic effect of crosscarmellose and sodium starch glycolate. The lag time for formulation FT8 was found to be 331min. and gives transit drug release as comparison of other formulation.

The FT-IR spectra of initial coated tablet compare with FT-IR spectra after 3month. There is no significant changes were observed hence it is concluded that the formulated coated tablets were stable and there is no interaction of excipient with drug after 3 months.

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