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Desire and Characterization of Compression Coated Pulsatile Drug Delivery System of Doxofylline for the Treatment of Asthma

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A B S T R A C T

In the present research work sustained release matrix, formulation of Doxofylline targeted to colon by using various polymers developed. To achieve pH-independent drug release of Doxofylline, pH-modifying agents were used. Colon targeted tablets were preparedin two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The pre-compression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. Among all the formulations F3 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 98.69% drug release. It followed zero order kinetics mechanism.

Keywords: Doxofylline, Colon targeteddrug delivery system, Ethyl cellulose, Eudragit L100, Eudragit S 100.

A R T I C L E I N F O

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1. Introduction

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a

prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. But there are certain conditions which demand release of drug after a lag time. i.e., Chronopharmacotherapy of diseases, which shows Circadian rhythms in their pathophysiology. Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. There are many conditions that demand pulsatile release like

a) Many body functions that follow circadian rhythm. e.g: Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
b) Chrono-pharmacotherapy of diseases, which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.
c) Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase as this tends to reduce their therapeutic effect.
d) The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.
e) Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.
f) The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite, and potential fooddrug interactions require delayed release of the drug to the extent possible.

All of these conditions demand for a time controlled therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by Pulsatile Drug Delivery Systems.

Diseases Requiring Pulsatile Delivery

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions.

Methods for Pulsatile Drug Delivery

Single unit systems

Capsular system

Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body. e.g.: Pulsincap® system. In this system a water insoluble body containing the drug formulation, system is closed with a swellable hydrogel. Plugged (insoluble but permeable &swellable) at open end. Upon contact with, gastrointestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position and dimensions of plug, control lag-time. For rapid release of water insoluble drug effervescent or disintegrating agents are added. Plug material is generally made up of following:

- Swellable materials coated with but¬ permeable polymer (polymethacrylates).
- Erodible compressed polymer (HPMC,¬ polyvinyl alcohol).
- Congealed melted polymer (glyceryl¬ mono oleate).
- Enzymatically controlled erodible¬ polymer (pectin).

Introduction Floating Pulsatile Drug Delivery System

The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation, etc. During the past few decades, numerous oral drug delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a specific period of time at a predetermined and controlled rate

1. It is evident from the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the gastrointestinal tract (GIT) for a prolonged and predictable period of time exists today
2. Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS)
3. Low- density systems
4. Raft systems incorporating alginate gels
5. Bioadhesive or mucoadhesive systems
6. High-density systems
7. Superporous hydrogels
8. Magnetic systems

The current review addresses briefly about theFDDS that is one of the most leading methodologies in gastro-retentive drugformulations.

2. Materials and Methods

Materials: Doxofylline, Sodium starch glycollate, different grades of eudragit polymers, talc, magnesium stearate.

Methodology

Analytical method development:

Determination of absorption maxima:

A solution of containing the concentration 10 µg/ ml was prepared in 0.1N HCl, 7.4 pH & phosphate buffer 6.8pH respectively, UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation calibration curve:

10mg of drug was accurately weighed and dissolved in 10ml of 0.1N HCl, 7.4 PH, and 6.8 PH in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4,6, 8, 10, 12, 14, 16, 18,and 20µg/ml with 0.1N HCl, 7.4 pH, and 6.8 pH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 273nm. Linearity of standard

curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

Pre-formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting.

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit.

Formulation development of Tablets:

Doxofylline pulsatile tablets were prepared by using compression coating technology. Initially internal core tabletcontaining drug and super disintegrate was formulated. For the prepared core tablet, compression coating is done by using various compositions of polymers. Ethyl cellulose, Polymethacrylate polymers such as Eudragit L100 and Eudragit S100 are used as polymers for compression coating.

Tablets are developed in two stages

1) Preparation of core tablet containing drug and super disintegrate.
2) Compression coating of prepared core tablets.

Formulation of core tablet:

The core tablets are formulated by using 250 mg of drug molecule, sodium starch glycollate as super disintegrate, microcrystalline cellulose as diluent, talc and magnesium stearate as Glidant and Lubricant respectively. The composition of core tablet was given in below table.

Table 1: Composition of core tablet

Ingredient Name	Quantity (mg)
Doxofylline	100
Sodium starch glycollate	31.25
Talc	5
Magnesium stearate	5
MCC pH 102	Q.S
Total weight	200

Total weight of core tablet was fixed as 200 mg. The tablets are prepared by using 9 mm flat punch. Then the prepared core tablets are subjected to compression coating by using various compositions of polymers.

Formulation of compression coated tablets:

The prepared core tablets were subjected to compression coating by using various compositions of polymers such as Ethyl cellulose, Eudragit L 100 and Eudragit S 100 as coating materials. The composition of coating layer is given in below table 2.Compression coating layer was divided into two equal portions i.e., 50mg of each quantity .Half of the quantity of powder blend was placed in the die cavity, core tablet was placed exactly in the middle of die cavity and then remaining quantity of powder blend was placed over the core tablet so that the powder blend should cover all the sides and top side of core tablet uniformly. Then the tablets are compressed by using 10mm flat surfaced punch using 8-station tablet punching machine with the hardness of 4-4.5 kg/cm^2.Then the prepared compression coted tablets are evaluated for various post compression parameters as per standard specifications.

Evaluation of post compression parameters for prepared Tablets

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviates by more than twice the percentage.

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness: Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness

for core and coated tablets is calculated and presented with deviation.

Friability: It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations).

***In vitro* drug release studies**

Drug release studies of Doxofylline core tablets:

The core tablets containing 100mg Doxofylline of were tested in (pH 6.8), for their dissolution rates. Dissolution studies were performed using USP paddle type sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzedspectrophoto-metrically at respective 270 nm.

Drug release studies of Compression coated Doxofylline tablets: The release of Doxofylline from coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme- free simulated intestinal fluid (SIF, pH 6.8) was used upto 12 hours to mimic colonic pH conditions.Drug release wasmeasured from compression coated Doxofylline tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm and 270 nm respectively. All dissolution runs were performed for six batches. The results were given with deviation.

3. Results and Discussion

The present study was aimed to developing compression coated Doxofylline formulations for colon targeting using ethyl cellulose and enteric coating polymers like Eudragit L100 and Eudragit S 100. All the formulations were evaluated for physicochemical properties and *in-vitro* drug release studies.

Analytical Method

Graphs of Doxofylline was taken in Simulated Gastric fluid (pH 1.2) and Simulated Intestinal Fluid (pH 6.8 and 7.4)

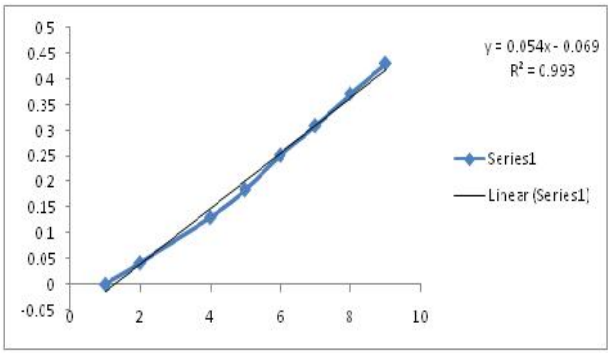

Figure 1: Standard graph of Doxofylline in 0.1N HCl

Table 3: Observations for graph of Doxofylline in 0.1N HCl (275 nm)

SNo.	Conc [mg/l]	ABS
1	1	0.001
2	3	0.075
3	4	0.128
4	5	0.199
5	6	0.280
6	7	0.343
7	8	0.397
9	11	0.557
10	12	0.623
13	21	0.823
14	22	0.87

Table 4: Standard graph of Doxofylline in 6.8 pH

S.No.	Conc [mg/l]	ABS
1	1	0.001
2	2	0.043
4	4	0.131
5	5	0.185
6	6	0.252
7	7	0.309
8	8	0.371
9	9	0.430
10	10	0.504
13	13	0.684
14	14	0.740
15	15	0.799
16	16	0.896

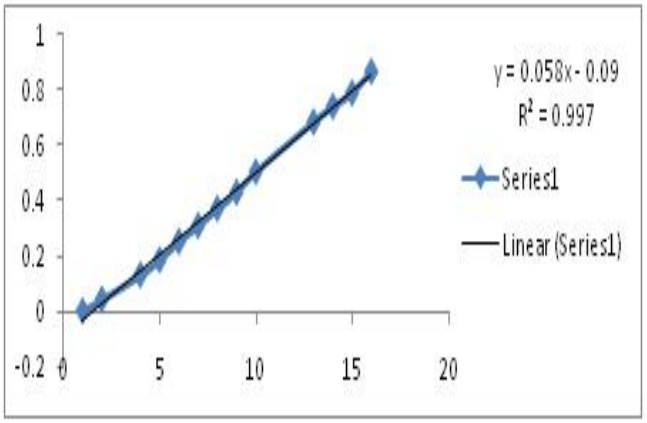

Figure 2: Standard graph of Doxofylline in 6.8 pH

Doxofylline blend was subjected to various pre-formulation parameters. The apparent bulk density and tapped bulk density values ranged from 0.52 to 0.581 and 0.606 to 0.671 respectively. According to Tables 7.4, the results of angle of repose and compressibility index (%) ranged from 32.74±0.12 to 37.08±0.96 and 13.37±0.38 to 14.72±0.62 respectively. The results of angle of repose (<35) and compressibility index (<23) indicates fair to passable flow properties of the powder mixture. These results show that the powder mixture has good flow properties. The formulation blend was directly compressed to tablets and *in-vitro* drug release studies were performed.

Quality Control Parameters For compression coated tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet. Total weight of tablet including core is 300 mg.

***In-Vitro* Drug Release Studies**

The compression coated tablets containing 200 mg of Doxofylline were tested in 6.8 pH phosphate buffer solution for their dissolution rates. The release of Doxofylline from compression coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme- free simulated intestinal fluid (SIF, pH 6.8) was used upto 12 hours to mimic colonic pH conditions. Drug release was measured from compression coated Doxofylline tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm ,319 and 320 nm respectively. All dissolution runs were performed for six batches.

From the dissolution, values it was evident that the formulations F3 & F9 were retarded the drug release up to 12 hours, they shown drug release of 98.69 and 96.45 % respectively. Formulations F1 –F3 contains ethyl cellulose alone. As the concentration of ethyl cellulose increases retardation nature was increased. F3 formulation containing 150 mg of ethyl cellulose was show almost negligible amount of drug release in first 3 hours from the 5th hour onwards it shown drug release as the time proceeds slowly the polymer was undergone erosion and allowed the drug to come out from the dosage form. The formulation was retarded drug release up to 12 hours and it showed maximum drug release in 12 hours i,e., in colon region. Similarly, the formulation F9 containing Eudragit L 100 in the concentration of 150 mg also showed similar drug release pattern.

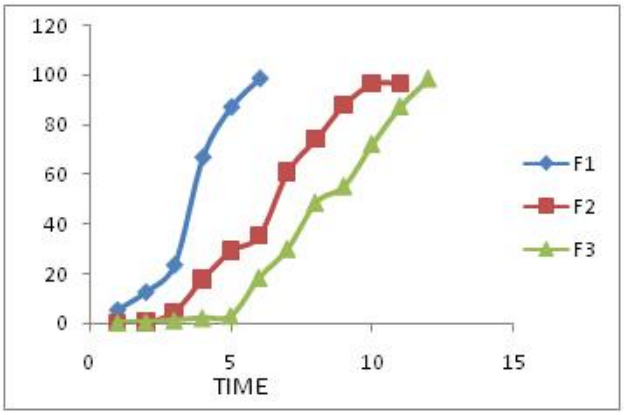

Figure 3: Dissolution of formulations F1-F3

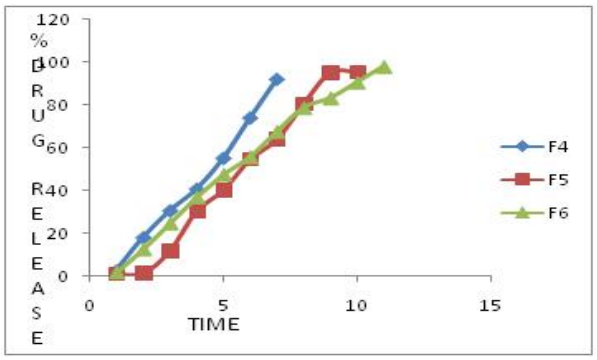

Figure 4: Dissolution of formulations F4-F6

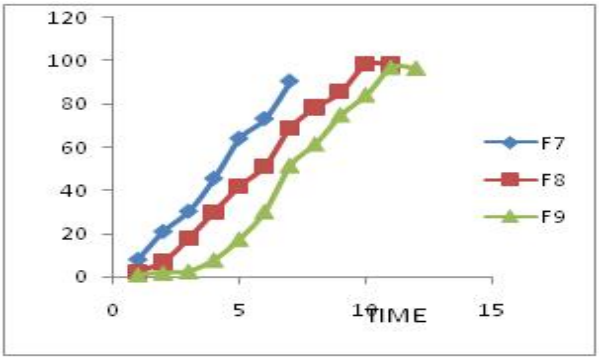

Figure 5: Dissolution of formulations F7-F9

Application of Release Rate Kinetics to Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

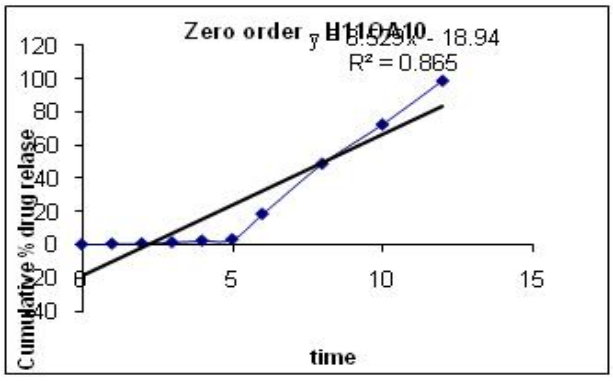

Figure 6: Zero order release kinetics graph

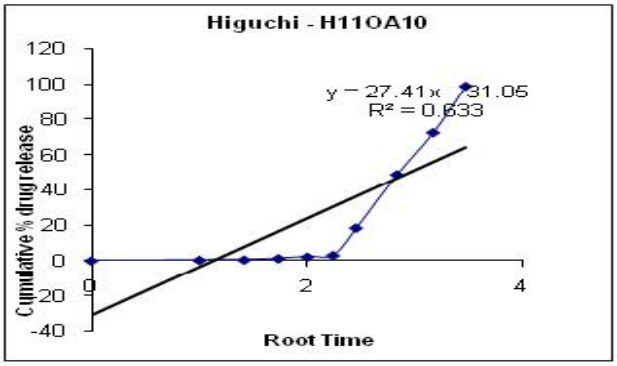

Figure 7: Higuchi release kinetics graph

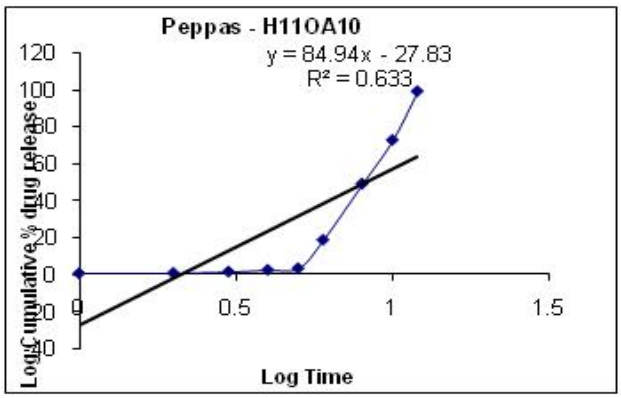

Figure 8: Kars Mayer Peppas graph

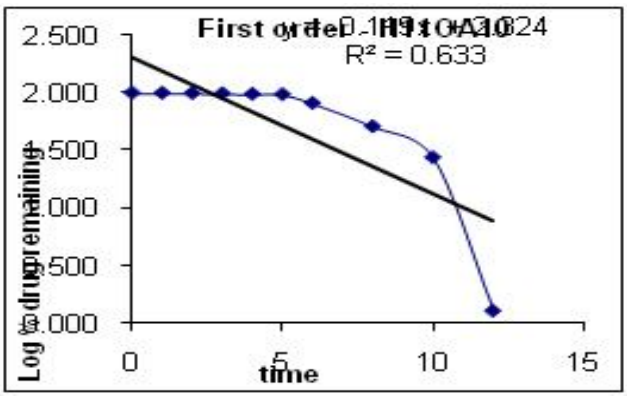

Figure 9: First order release kinetics graph

Table 2: Composition of coating layer

Ingredient name	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethyl cellulose (mg)	25	50	-	-	-	-	25	-	25
Eudragit S100 (mg)	-	-	25	50	-	-	25	25	-
Eudragit L100 (mg)	-	-	-	-	25	50	-	25	25
Magnesium stearate (mg)	3	3	3	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3	3	3	3
MCC pH 102 (mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	100	100	100	100	100	100	100	100	100

Table 5: Pre-formulation parameters of core material

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	36.01	0.55	0.645	14.72	0.85
F2	34.8	0.57	0.66	13.63	0.86
F3	32.74	0.53	0.606	14.19	0.858
F4	35.33	0.531	0.613	13.37	0.866
F5	36.24	0.549	0.641	14.35	0.856
F6	36.12	0.564	0.666	15.31	0.846
F7	37.08	0.581	0.671	13.41	0.865
F8	35.12	0.567	0.654	13.12	0.845
F9	35.45	0.571	0.689	13.28	0.855

Table 6:*In-vitro* quality control parameters for compression coated tablets

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	312.5	4.5	0.52	4.8	99.76
F2	305.4	4.2	0.54	4.9	99.45
F3	298.6	4.4	0.51	4.9	99.34
F4	310.6	4.5	0.55	4.9	99.87
F5	309.4	4.4	0.56	4.7	99.14
F6	310.7	4.2	0.45	4.5	98.56
F7	302.3	4.1	0.51	4.4	98.42
F8	301.2	4.3	0.49	4.7	99.65
F9	298.3	4.5	0.55	4.6	99.12

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table 7: *In-vitro* Drug Release profile for coated formulations (F1-F9)

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	5.42	0.26	0.34	2.39	1.11	1.44	8.06	2.65	1.32
2	12.65	0.44	0.54	17.88	1.29	12.30	20.94	7.23	2.14
3	23.56	4.65	1.26	30.45	11.71	24.44	30.26	18.19	2.90
4	66.8	17.87	2.22	40.59	30.22	36.61	45.44	30.27	8.11
5	86.9	29.18	3.05	55.01	40.18	47.30	63.86	42.06	17.72

6	98.35	35.45	18.41	73.85	54.53	55.68	72.93	51.40	30.40
7		61.04	30.05	91.92	63.88	67.53	90.23	69.13	51.64
8		74.24	48.69		80.53	78.72		78.45	61.59
9		88.13	55.38		95.06	83.34		85.67	74.97
10		96.39	72.34		95.18	90.67		98.45	84.18
11		98.45	87.56			98.12		98.12	91.87
12			98.69						95.45

4. Conclusion

In the present research work sustained release matrix, formulation of Doxofylline targeted to colon by using various polymers developed. To achieve pH-independent drug release of Doxofylline, pH-modifying agents (buffering agents) were used. Pulsatile tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The pre-compression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F3 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 98.69% drug release. It followed zero order kinetics mechanism.

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