Original Research Article

~~Fabrication,~~ Formulation and Evaluation of Doxofylline Sustained-Release Tablets by using Chitosan and Guar Gum as ….

ABSTRACT

Put some introduction first …

Aim- The aim of the present investigation was ~~done for the purpose~~ to ~~fabricate, manufacturing,~~ formulate and evaluate~~ing~~ Doxofylline sustained action tablets by using different concentrations of Chitosan and Guar Gum.

~~**Place and Duration of Study**- This work is done in Post graduate laboratory of SND College of Pharmacy, Yeola, Dist Nashik, Maharashtra, India.~~

Method- Factorial design was used to prepare Doxofylline sustained-release tablet. Doxofylline sustained-release tablets were prepared employing different concentrations of Chitosan, Guar Gum, Lactose, and Magnesium Stearate in different combinations by direct compression technique. Total 9 formulations were designed, formulated and evaluated for the hardness, thickness, friability, % drug content and *in-vitro* drug release.

Results- A study of the release of drug by *in-vitro* found that F8 is found to be best efficient formulation which consisting of both Chitosan and Guar Gum, delayed the release of drug up to 24 hours and performs excellent release of drug in starting hours of drug release in the body. The drug released from F8 formulation indicates the kinetic model of First Order, by anomalous diffusion. Different studies of stability were performed based on ICH guidelines. The formulation F8 at 40ºC±2 /75 % ±5 RH shows no major change relegated to assay and drug release pattern which indicate stable prepared formulation.

Conclusion- This study conclude that by using natural polymer better drug release is observed in above study. Doxofylline in combination with chitosan and guar gum shows good release and better dissolution rate as compare with single polymer. This formulation has better scope in future for further release studies.

Keywords: *Chitosan; Doxofylline; Guar gum; HPLC; Sustained-release*

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Comment [A1]: Generally, the abstract section is better if re-written

Comment [A2]: Start the abstract with a brief introduction which then could lead you to your objective (aim). I think it would be better if you read some abstracts of Articles.

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Comment [A3]: Why factorial design? Did you conduct an optimization study? Nothing was mensiond about this in the method and even in the result and discussion section?.

Comment [A4]: The method is not discussed in the method section

Comment [A5]: This was not included in the method and the resulr and discussion part.

Comment [A6]: What above study?

Comment [A7]: How can you conclude for a study you did not conduct? I haven't seen a formulation with chitosan or guar gum only.

Comment [A8]: What do you mean by this?

Comment [A9]: Do you think HPLC is a key word for your study?

1. INTRODUCTION

Most of the traditional oral measurement structures like tablets and cases are detailed to deliver the dynamic medication following oral organization, to get quick and complete foundational drug assimilation. Such prompt delivery items bring about moderately fast medication retention and beginning of going with pharmacodynamics impacts. In any case, after retention of the medication from the structure of the measurement is finished, plasma drug fixations decrease as per the medication's pharmacokinetic profile [1]. At long last, plasma drug fixations fall underneath the base successful plasma focus, bringing about loss of remedial movement. Before this point is reached, another portion is normally given if a supported restorative impact is wanted. An option in contrast to overseeing another portion is to utilize a dosing structure that will give supported medication discharge, and accordingly keep up plasma drug fixations, past the thing is regularly seen utilizing quick delivery measurement structures. As of late, different adjusted delivery drug items were created for controlling the delivery pace of medication, additionally, become ideal opportunity to drug discharge. An adjusted delivery is characterized to person for which the medication discharge qualities of time course and additionally area is picked to achieve helpful or comfort targets not offered by customary dose structures like balms, or fast-dissolving dose forms [2] [7].

Comment [A10]: This statement does not give sense at all in relation to your work. What is oral measurement structure? What is drug assimilation? ..... I think you have used words just to eskape plagiarism!

Comment [A11]: What is this?

Comment [A12]: What is this

Comment [A13]: Generally the writup is hard to grasp the point you wanted to depict here!

Sustained-release drug delivery

Sustained-release drug delivery can show predetermine release by maintaining sustained medication activity at a specified rate while minimizing undesired side effects by keeping a reasonably same, efficacy level of drug in the body [6] [8]. Local effect of the drug-related to diseased tissue by keeping the controlled release system in space. Different carriers and particles are used to transfer the drug to the target organ. Many oldest dosage forms ~~namely~~ such as suspension, emulsion, tablet and capsule, ~~and suppositories, etc.~~ have a few drawbacks, like drug having a short half-life need repeated drug administration, which increases the like hood of skipping a dose of a drug resulting in fewer patient compliance [5] [9]. Drug's steady-state level cannot be maintained in the body because of peak-valley due to absorption and elimination of the drug from the body and this would lead to underdose or overdose, as uniform drug amount increases or decrease above the range of therapeutic. When an overdose occurs, changing drug levels may precipitate undesirable consequences, especially if the substance has a small therapeutic index [3].

Merits of Sustained-release Dosage Form

Sustained-release dosage form gives a long-term therapeutic effect by continuously releasing the drug. It reduces frequent dosing of drugs and gives prolong the action [11]. It provides patient compliance. It does not require any special storage conditions and handling precautions. Drugs having nauseous taste and smell can be given by the above formulation. It reduces local side effects by reducing the total amount of drugs. The more stable dosage form as compared to others [4].

Types of Sustained Action Systems

A) Diffusion Controlled System

I. Reservoir Storage System: The inner raw part of the drug is covered by polymer material. Drug release is dependent upon the nature of the membrane. It is possible to release the drug by Zero Order by this system. Those molecules which have high molecular weight have low delivery by using this type of device.

II. Matrix Devices: This consists of an appropriate combination of a drug molecule with a polymer matrix. Those compounds having high molecular weight can be easily delivered by this device.

B) Dissolution Controlled Release System

I. Matrix Release System: Drugs are surrounded by a slowly dissolving polymer membrane. The drug also got protection from other things.

II. Encapsulation Dissolution Control: Similar to microencapsulation by coating seeds, granules, and particles.

C) Diffusion and Dissolution Controlled System: Used for those drugs which have high doses and low half-life. The drug is uniformly mixed with matrix and release drug either swelling, hydrolysis, or using enzymatic attack. By imbibing mechanism or by addition of hydrogen or by enzyme action [12] [13].

Drug Removal Mechanism by Matrix Tablet

In a biodegradable matrix system, drug release is determined by polymer erosion from the matrix surface; whereas in hydrophilic matrices gel layer is formed and it depends upon time-release functions. The thickness of the layer of gel will determine the diffusion path length of drug molecules. As soon as swelling continues gel becomes thick and it results in slow drug release from polymer; but, because of regular hydration polymer gets disintegrated from the

matrix surface which results in reducing the depilation area and increasing the rate of dissolution in the same system.

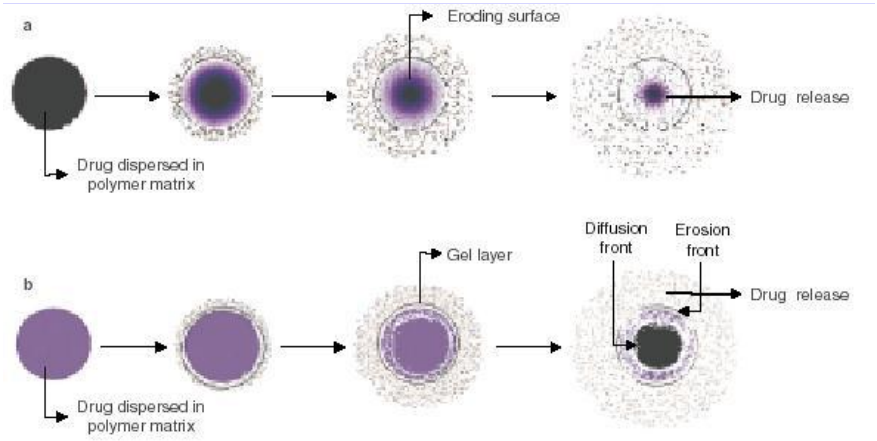

Figure 1. Hypothetical Diagram shows release of drug from diffusion controlled drug delivery system. In which there is homogenous mixture of polymer matrix (a) and hydrophilic, swellable polymer matrix (b).

Comment [A14]: Figures should be cited intext. Is this diagram your own drowing or cited from others work?

Kinetics for Drug Release-Suitable Model for Drug release Data

Once a newer formulation enters the market from the manufacturer, it is mandatory to crosscheck that its dissolution is in a good manner. Different research and development laboratory and industry keep their eyes on drugs dissolution studies. Drug dissolution from the dosage form is studied by the different kinetic models. in which the mixed quantity of drug (Q) is a work of test time, t or Q=f(t). Few scientific meanings of the Q(t) function are rarely used, such as zero order, first order, Hixson–Crowell, Higuchi, Korsmeyer–Peppas models.

Zero Order Kinetics

Drug released in the same amount from any pharmaceutical formulation by the particular slot of time and this one is the best technique for removal of the drug to reach long pharmacological effect, this is elaborated by the given formula-

$$Qt = Q0 + K0t$$

Where Qt means the quantity of drug release from the formulation in time t.

Q0 is starting quantity of drug in a liquid.

K0 is Constant for Zero Order Release.

The drug release values are plotted on a graph in the form of the cumulative amount of release of drug Vs time. Mostly used for many new modified release dosage forms and matrix tablets or patches dosage forms.

First Order Kinetics

Such a type is widely used for the absorption and elimination of many drugs.

$$\text{Log } Qt = \text{Log } Q0 + (K1/2.303)$$

In the above equation, Qt denotes the amount of drug release within time t, Q0 is starting quantity of drug release from formulation, K1 is the first-order release constant.

The above-obtained data were plotted on a graph as Log cumulative % of drug remaining Vs time which shows a straight line with the slope as – K/2.303.

This formula is utilized for drug absorption in pharmaceutical dosage form, those containing water-soluble drugs in porous form.

Higuchi Model

Only one model describes the release of drugs from the matrix system. Model depend depends on the various hypothesis that the concentration of drug initially is higher than its solubility. Diffusion of the drug takes place in only one direction. Higuchi explains the release of drugs depends upon scientist Fick's First Law square root dependent.

$$Ft = Q = KH/t$$

Where KH is Higuchi Dissolution constant.

Hixson-Crowell model

Hixson and Crowell (1931) noted that the area of the granular side of particles is proportional to the cubic root of its volume which is derived by the equation described in the following manner.

$$W0\ 1/3 - Wt\ 1/3 = Kst$$

Mechanism of Drug Release

To determine the drug release mechanism resulting from swelling (due to hydration) and gradual matrix erosion, the first 60% of drug release data can be fitted into the Korsmeyer–Peppas model, which is frequently used to describe drug release behavior from polymeric

systems when the mechanism is unknown or when multiple types of release phenomena are present.

$$\text{Log } (Mt / M\infty) = \text{Log } KKP + n \text{ Log } t$$

Where, Mt Quantity of drug release at specific time t, M∞ quantity of drug removes at the infinite time; KKP drug release rate constant related to physical and mechanical properties of the tablet, and n is the release exponent indicative of the mechanism of drug release [10].

Comment [A15]: This all statement is already summarized in the table. No need for repetation.

Table 1. Drug release Kinetic

Model Name	Relation	System following the Model
First Order	Log Qt= Log Q0+ (K1/2.303)	Drugs that are soluble in water
Zero Order	Qt = Q0 + K0t	Beneath the Skin system and Osmotic systems
Higuchi	Ft= Q= KH/t	Matrix Formulation Erodible isometric matrices
Hixon- Crowell	W0 1/3-Wt 1/3 = Kst	

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Where,
ft = Amount of Drug remove from the system at Time t.
KH, Ko, and Ks = constant of the Drug release rate of a particular model
Qo = Remaining quantity of drug to be released at zero order
Qt = Quantity of drug remain to release at time t
Wo= Starting Quantity drug present in the matrix;
Wt = Quantity of released at time t

Advantages of Doxofylline SR over Theophylline SR:

- Sustained bronchodilation for 24 hours including controlling of inflammatory cytokines release.
- More selective inhibition of phosphodiesterase activities than theophylline reduces the affinity with A1 and A2 Adenosine Receptors.
- Long action even prevents nocturnal asthma attacks.
- Devoid of cardiovascular, central nervous, and gastrointestinal side effects.
- Asthma is a chronic disease, once-daily dosing will increase patient's compliance [14].

Comment [A16]: This should be well referenced and made in to paragraph. Avoide bulletins in scientific articles.

2. MATERIALS AND METHODS

Comment [A17]: Generally, the most important part of your study, the method, is poorly presented.

2.1 Preparation of PH 6.8 Phosphate Buffer

2.2 Formation of the standard graph

2.3 Preparation of Doxofylline Coe Tablet

Table 2. Formula for Doxofylline Tablet

Drug with Additives	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
					Mg/Tablet				
Doxofylline	800	800	800	800	800	800	800	800	800
Chitosan	20	20	20	30	30	30	40	40	40
Guar Gum	20	30	40	40	30	20	20	30	40
Lactose	45	35	25	15	25	35	25	15	05
Talc Powder	10	10	10	10	10	10	10	10	10
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Alcohol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Final Weight	900	900	900	900	900	900	900	900	900

2.4 Evaluation parameter of material undergo compression

2.4.1 Angle of Repose

2.4.2 Determination of Bulk Density and Tapped Density

2.4.3 Compressibility Index (Carr's Index)

2.4.4 Hauser's Ratio

2.5 Evaluation parameter of martial undergone compression

2.5.1 Weight Variation in Tablet

2.5.2 Tablet Thickness

2.5.3 Hardness of Tablet

2.5.4 Friability of Tablet

2.5.5 Content of Active Drug in tablet

2.5.6 Drug Release Study (*In-vitro*)

2.5.7 Kinetics of Dissolution Data

2.5.8 Drug Release Mechanism

3. RESULT AND DISCUSSION

3.1 Organoleptic Properties

The properties of Doxofylline showed similar results reported in IP. It is concluded that Doxofylline is in a pure state.

Table 3. Observation of Organoleptic Properties of Doxofylline

Identification Test	Reported Standards	Result of Sample Obtained
Appearance	Crystalline Powder	Crystalline Powder
Colour	White Colour Powder	White Colour Powder

Comment [A18]: Where are the methods?

Comment [A19]: The table number should be cited in text. Otherwise why do we need a number?

Comment [A20]: What was your basis to select this ranges for Guar gum and Chitosan (20-40)

Comment [A21]: What was the purpose of alcohol?

Comment [A22]: Change this subtitle in to something that will represent what is done. Such as pre-compression powder blend evaluation …or …

Comment [A23]: The methods should be presented. How were the procedure conducted and … which reference … method or Pharmacopoea did you use?

Comment [A24]: Not included in the method part.

Comment [A25]: The methods used to conduct this study should be dipiocted in to the method section.

Odor	Odorless	Odorless

Table 4. Melting Point

Sr.No.	Parameter	Drug
1	Melting Point (Sample)	144^0C – 146^0C
2	Melting Point (Reference)	142^0C – 146^0C

3.2 API Characterization

The drug must be tested for various physicochemical tests which are listed in table 5.

Table 5. Physical Properties of Drug

Sr.No.	Parameter	Result
1	Bulk Density	0.562 gm/ml
2	Tapped Density	0.624 gm/ml
3	Compressibility Index	11.03%
4	Hauser's Ratio	1.110
5	Angle of Repose	28^0

Drug complies with all specifications based on the above result and concluded that drug has very good flow properties.

3.3 Infrared Spectra of Doxofylline

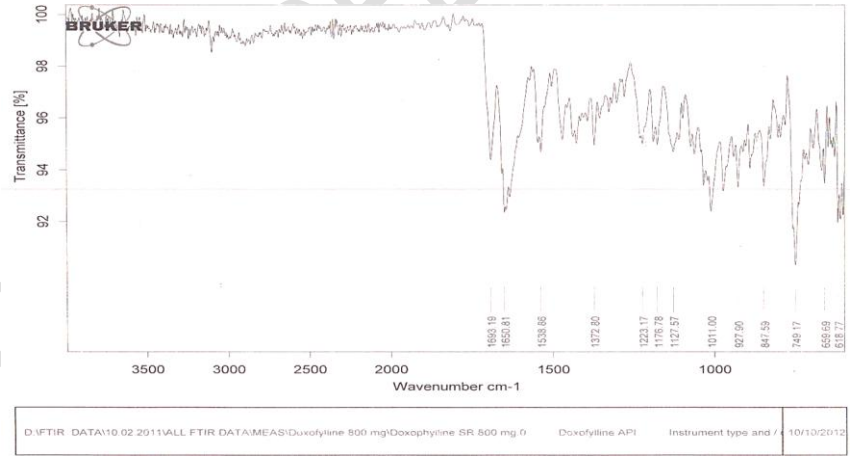


Figure 2. IR Graph of Drug Doxofylline

Comment [A26]: I think the organoleptic properties are also part of the API characterization.

Comment [A27]: What decision did you made based on the data depicted in this table in your study. Or whay did you conduct this studies?

Comment [A28]: The method for the compatability study should be depicted in the method section.
The result from the FTIR and DSC are poorly interpreted.
How do you comeup with that the components are compatible from the FTIR and the DSC?

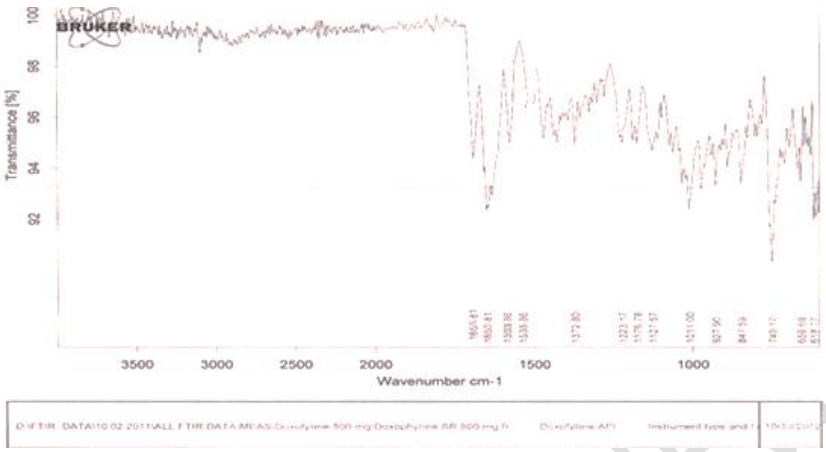


Figure 3. IR Graph of Drug Doxofylline + Polymer

Table 6. Interpretation of IR Bands of Doxofylline

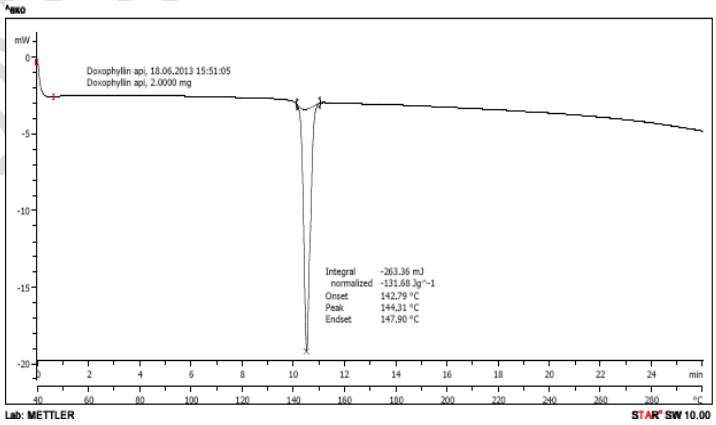
Groups	**Std. Freq. (cm^{-1})**	**Observed Freq. (cm^{-1})**
C-H Stretch	3130-3070	3110.10
C-H Stretch	1090-1010	1011.00
C-H Stretch	1700-1690	1693.19
C-H Stretch	1680-1620	1650.81
C-O-C	1140-1070	1127.57

Table 7: Interpretation of IR Bands of Doxofylline + Polymer

Groups	**Std. Freq. (cm^{-1})**	**Observed Freq. (cm^{-1})**
C=N Stretch	1500-1600	1595.20
C=C Stretch	1680-1620	1656.10
C-H Stretch	1400-1500	1430.00

Comment [A29]: This we can not call an interpretation. It is just a presentation of values from FTIR study. This comment also applies for Table 6.

3.4 Differential Scanning Calorimetry (DSC):



Comment [A30]: The figures from the DSC does not depict which one is which. Physical mixture of what and what?
Which fig. is for the pure and which one for the mixture

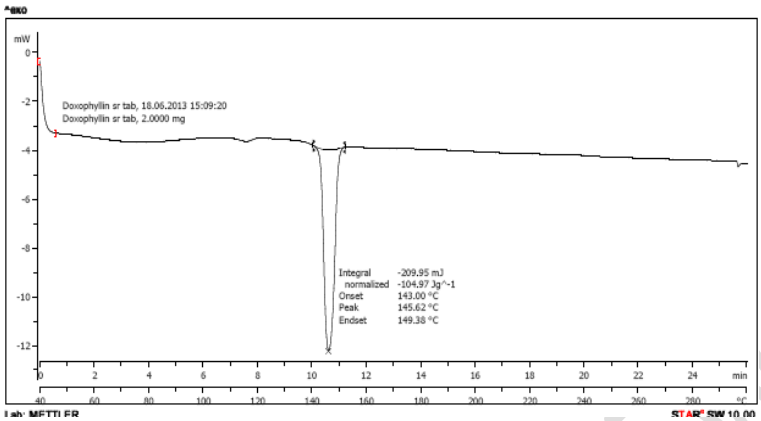


Figure 4. DSC of Physical Mixture

The above graph indicates that DSC data confirmed the API and all other additives are compatible with one another.

Comment [A31]: How is that confirmed? What did you observe in the figures to conclude that?

3.5 Solubility:

Table 8. Solubility Data of Doxofylline

Sr. No.	Water	Drug Dissolved(mg/ml)
1	Water	0.014
2	0.1 N HCL	0.025
3	Phosphate Buffer of PH 6.8	0.018

According to the above results, 0.1N HCL shows more solubility than other media for that 0.1N HCL used further study.

3.6 Calibration Curve of API in 0.1N HCL:

Table 9. Drug Absorbance in 0.1 N HCL

Quantity of Drug (µg/ml)	Absorbance (nm)
9	0.3044
13	0.4767
18	0.6916
22	0.8457
26	0.9791

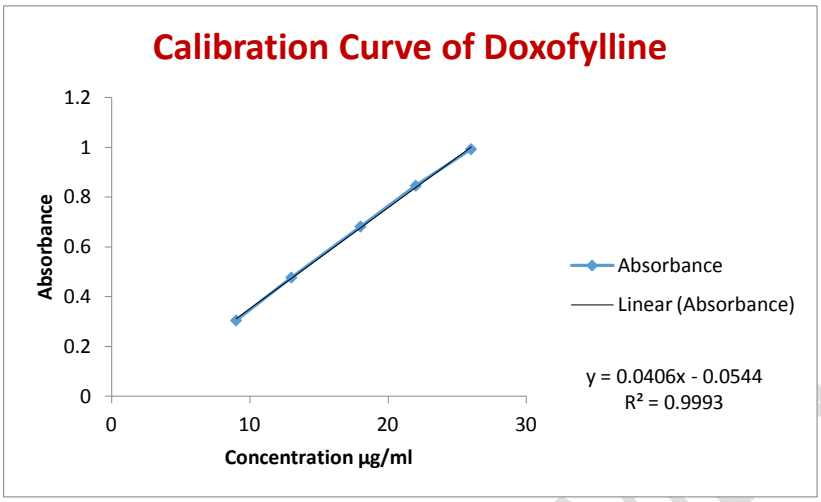


Figure 5. Calibration Curve of Doxofylline by UV

Observation:

From the Calibration curve Line Equation is given as

Y =0.04x - 0.044

The value of R2 is 0.999 by obtaining the result it has been concluded that API Obeyed Beer-Lambert's Law.

Comment [A32]: Y=0.04x – 0.054 is depicted on the calibration curve

Comment [A33]: What is obeyed from the Beer-Lambert's law?

UV Spectrum of Doxofylline

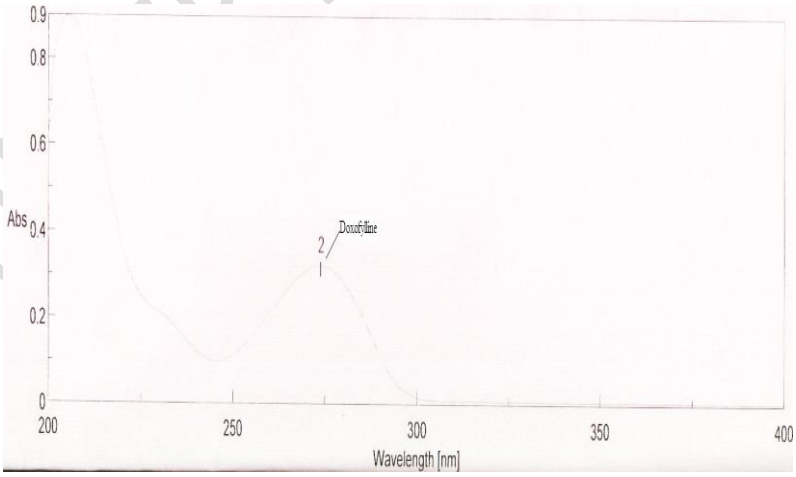


Figure 6. UV Spectra of Doxofylline

Doxofylline spectrum (λmax) was found at 274 nm.

3.7 API Potency calculation:

Assay = 99.13% **LOD:** 0.17%

The quantity depends upon 100% w/w assay.

$$\frac{\text{Strength X100 X 100}}{\text{(Assay Depends on Loss in LOD) X (100 \% LOD)}}$$

$$\frac{\text{800 X 100 X100}}{\text{(99.13) X (100 – 0.17\%)}} = 805.6 \text{ mg.}$$

Dispensing of Doxofylline was done based on potency calculation.

Analytical method:

As per IP assay on a dried basis was found to be 99.3 %.

3.8 Drug-Excipient compatibility study data:

Table 10. Drug Absorbance in 0.1 N HCL

Sr. No.	Physical Admixture	Drug Excipient Ratio	Initial Description	Observation 40ºC/75%RH		
				1St Week	2nd Week	4th Week
1	Doxofylline API	Plain API	White Powder	No Change	No Change	No Change
2	Doxofylline + Chitosan	1:1	White Powder	No Change	No Change	No Change
3	Doxofylline + Guar Gum	1:1	White Powder	No Change	No Change	No Change
4	Doxofylline + Lactose	1:1	White Powder	No Change	No Change	No Change
5	Doxofylline + Purified Talc	1:1	White Powder	No Change	No Change	No Change
6	Doxofylline + Mg Stearate	1:1	White Powder	No Change	No Change	No Change
7	Doxofylline + Alcohol	1:1	White Powder	No Change	No Change	No Change

Comment [A34]: Is this value the same as the value presented in the "Analytical method" 99.3?

Comment [A35]: Where or how did you get this value?

Comment [A36]: Where is this equation cited from?

Comment [A37]: What is this value …. Is this assay for the API? ….. the paper has major flow (order) problem. Please try to reorganize according to the procedure steps.

Comment [A38]: According to which method did you conduct this study? Overmore the method is not clear ….

Comment [A39]: Did you check for absorbance or Color?

3.9 In-process results:

In process Evaluation of in compression blend

Table 11. Evaluation of Blend before Compression

Batch No.	Bulk Density (mg/ml)	Tapped Density (mg/ml)	Compressibility Index (%)	Hauser's Ratio	LOD %
F1	0.495	0.590	19.19	1.191	1.23
F2	0.469	0.533	13.64	1.136	1.04
F3	0.458	0.521	13.75	1.137	0.97
F4	0.468	0.545	16.45	1.164	1.16
F5	0.464	0.527	13.57	1.135	0.81
F6	0.576	0.679	17.40	1.178	----
F7	0.558	0.681	22.04	1.223	----
F8	0.632	0.790	25.00	1.250	----
F9	0.561	0.676	20.49	1.204	----

Comment [A40]: Why are this results missing

All the above values are means ± SD (n=3)

Comment [A41]: Where are the SDs?

Above all formulation shows good flow properties.

Comment [A42]: Discuss with specifications rather than just saying all formulations showed good flow … what about tha LOD?

In-process Evaluation of Tablet

IPQC Test

Table 12. In Process Evaluation of Tablet

Batch No.	Average Weight(mg) (n= 10)	Thickness (mm) (n= 5)	Hardness (N) (n= 5)	Friability (%)
F1	899±2.05	5.28±0.008	186±1.34	0.240
F2	901±2.83	5.29±0.114	195±1.22	0.177
F3	898±2.31	5.28±0.013	177±1.87	0.119
F4	899±2.95	5.30±0.011	197±1.30	0.175
F5	897±2.22	5.28±0.013	189±1.51	0.118
F6	1046±2.60	6.00±0.013	293±1.64	0.329
F7	1045±2.53	6.05±0.012	298±1.30	0.468
F8	1048±1.59	6.01±0.016	289±1.30	0.400
F9	1046±2.37	6.04±0.023	296±1.87	0.334

Comment [A43]: The target weight was 900mg why is this significant weight gain for the formulation F6 to F9? It would be difficult to compare the tablets while there is significant weight difference?

All the above values are means ± SD (n=3)

Above all batches has passed all parameters like thickness, Variation in weight, Hardness of Tablet, Friability shows it within the limit.

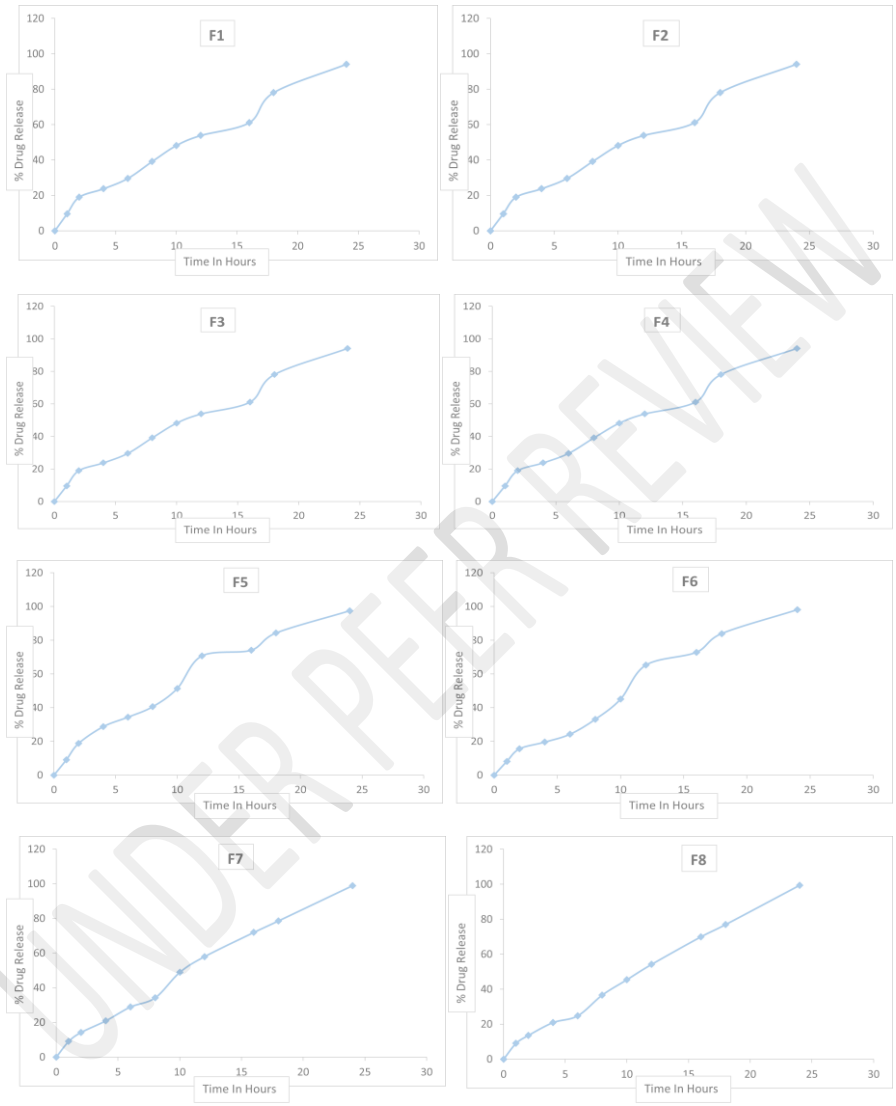
3.10 Dissolution Results of Formulations:

Table 13. Comparative Dissolution Profile for F1-F9 Formulation

Formula Code	% Drug Release (In Hours) Percent drug release at the time (hrs)									
	1	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**18**	**24**
F1	8.47 ±0.25	15.14 ±0.21	22.92 ±1.32	33.12 ±2.26	47.82 ±2.78	53.42 ±2.96	61.15 ±4.61	73.21 ±1.02	84.70 ±2.78	91.60 ±2.3
F2	8.80 ±1.56	15.24 ±1.50	20.85 ±2.04	34.24 ±1.63	40.70 ±4.3	53.88 ±1.74	66.79 ±2.93	75.08 ±2.20	84.26 ±4.30	90.50 ±2.20
F3	9.34 ±3.02	21.34 ±3.02	30.54 ±1.06	48.07 ±3.05	57.30 ±3.05	64.88 ±2.40	70.35 ±2.03	78.97 ±2.0	86.36 ±3.05	95.38 ±2.01
F4	9.56 ±2.94	19.01 ±2.42	23.74 ±1.00	29.57 ±2.03	39.11 ±1.00	48.19 ±1.92	53.84 ±1.09	61.10 ±1.2	78.04 ±1.00	94.16 ±2.20
F5	9.08 ±4.01	18.84 ±4.01	28.78 ±3.29	34.40 ±3.45	40.54 ±1.13	51.36 ±1.8	70.70 ±2.93	74.09 ±2.322	84.26 ±2.30	97.48 ±2.30
F6	8.16 ±1.98	15.62 ±1.98	19.60 ±2.92	24.26 ±0.94	33.10 ±1.3	45.03 ±3.00	65.23 ±3.01	72.83 ±1.20	83.91 ±1.30	98.08 ±1.31
F7	9.02 ±1.34	14.21 ±1.21	20.89 ±2.34	28.91 ±3.20	34.16 8±1.2	48.88 ±2.35	57.93 ±1.13	71.93 ±2.10	78.60 ±1.20	98.93 ±1.10
F8	09.00 ±2.12	13.55 ±2.03	20.90 2.20	24.75 ±2.21	36.66 ±3.23	45.42 ±1.13	54.17 ±2.10	69.93 ±2.500	76.93 ±3.24	99.35 ±2.15
F9	9.24 ±2.32	16.38 ±2.20	21.60 ±2.12	26.3 ±1.26	35.83 ±1.40	46.18 ±2.23	56.33 ±3.21	72.48 ±1.6	81.64 ±1.41	98.87 ±3.20

All the above values are means ± SD (n=3)

Drug Release for F1- F9 Formulation



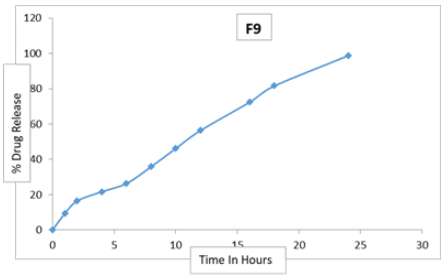


Figure 7. % Drug Release for F1- F9 Formulation

Drug Release Kinetics

Data received by studying drug release, above parameters were followed zero-order, first-order, Higuchi, Kosermayer's for the establishment of the release of drug mechanism and Drug release Kinetic of prepared tablet formulation. A regression coefficient (r^2) indicated the proper model for the formulation and is the important criteria for the selection of the model.

To find the drug release mechanism above data is analyzed by Zero Order Kinetic, First Order Kinetic, Higuchi's, and Korsmeyer equations.

Table 14. Dissolution model for F1- F9 Formulation for R^2 Value

Sr. No.	Zero Order Model	First – Order Model	Higuchi Model	Kosmeyer Model Papa's Model	Hixon and Crowel Model
1	0.9727	0.9616	0.9688	0.7836	0.9931
2	0.9528	0.9779	0.9578	0.7836	0.9854
3	0.9196	0.9756	0.9844	0.7836	0.9934
4	0.9821	0.8756	0.9525	0.7836	0.9481
5	0.9661	0.8900	0.9660	0.7836	0.9699
6	0.9769	0.8234	0.9185	0.7836	0.9407
7	0.9920	0.7717	0.9424	0.7836	0.9207
8	0.9960	0.7203	0.9341	0.7836	0.8915
9	0.9922	0.7736	0.9332	0.7836	0.9190

The most suitable and fitted model was found to be Zero Order Kinetic Model.

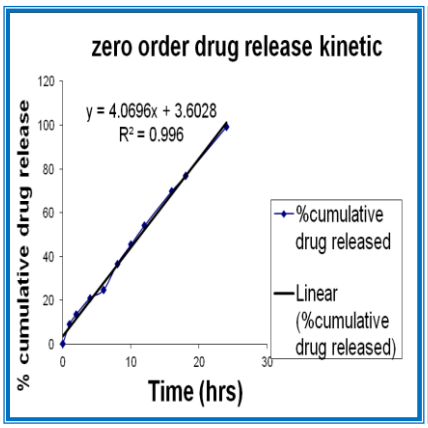


Fig 8

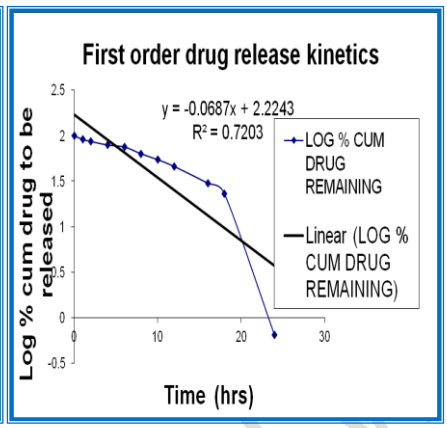


Fig 9

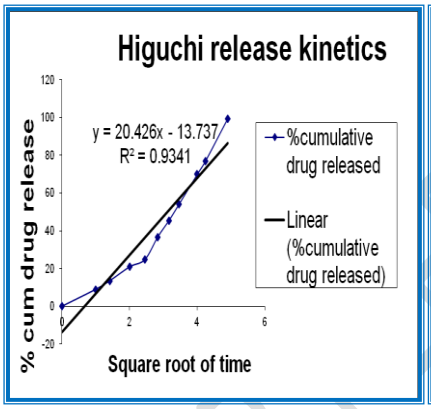


Fig 10

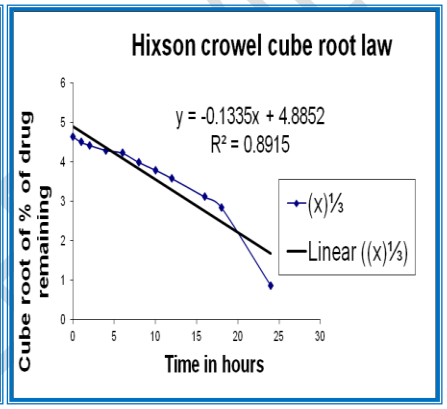


Fig 11

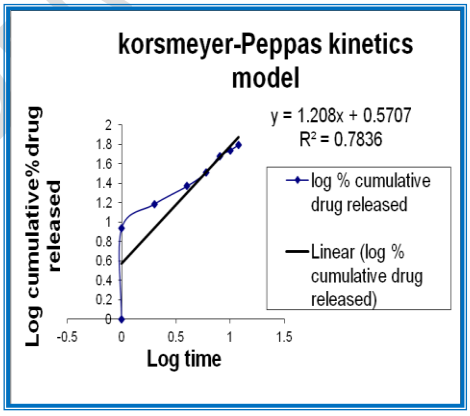


Fig 12

4. CONCLUSION

In this way, Doxofylline sustained-release tablets were prepared and developed, by using different combinations of natural polymers like Chitosan and Guar Gum (release retarding polymers). ~~Doxofylline is broadly utilized in the treatment of patients suffering from COPD (Chronic Obstructive Pulmonary Disease). Sustained-release tablets of Doxofylline are rarely available in the market hence we have selected the drug for formulation.~~ The tablet containing Doxofylline were prepared by wet granulation technique. From the physical evaluation, FTIR, in which stretching vibrations are observed, C=C at 1650 cm-1, C-O-C at 1127 cm-1, C-N at 1011 cm-1, UV shows spectrum (λmax) at 274 nm, and DSC studies show Sharp Peak at 1440c, hence the identified drug is Doxofylline. By studying stability, and DSC study we observed that API and additives are compatible with each other. There should not be any interaction between API and additives. We observed the melting point of the above formulation in the range of 144^0C to 148^0C. Tablets were prepared by using chitosan and guar gum as natural polymer using the wet granulation method of tablet manufacturing. ~~We have also added lactose as diluents, alcohol as a binding solution and talc as a lubricant, and magnesium stearate as a glidant.~~ Prepared tablets were evaluated using parameters such as physicochemical parameters like Hardness of the tablet, friability, average weight of the tablet, the thickness of tablet, and drug content, all these indicate that prepared tablets were physically and mechanically stable also comply all the necessary parameters as per pharmacopeia. From the dissolution studies formulation, No F8 showed 99% drug release that complies with IP. The stability testing of formulation No F8 at 40ºC±2 /75 % ±5 RH revealed no specific changes related to assay and release of drug pattern which indicates the stability of the prepared formulation. Used polymers Guar Gum and Chitosan show good release as that of synthetic polymer. At last, it has been concluded that the method used for manufacturing of above formulation meets all the stated specifications as well as quality parameters. This technique will produce reproducibility and robustness in the prepared formulation.

Comment [A44]: You said the tablets were prepared by direct compression?

5. FUTURE SCOPE

The above research work has several scopes in the future for developing new drug formulations and study of different natural polymers as we have used in the above project. Also, different methods were used for formulation instead of wet granulation. There are

different ways to treat chronic pulmonary obstructive disease and asthma therefore various formulations are also made in the future for the betterment and curing of this disease.

Certain future scopes like bioequivalence study of various formulations, manufacture and develop new techniques for release pattern of the drug by using a combination of polymers and advanced new drug delivery can be used for the above project.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

STUDY SIGNIFICANCE

The study highlights the release of the drug more slowly into the bloodstream due to use of polymers, which provides the ability to maintain a constant level of medicament in the body.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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