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Formulation and Evaluation of Doxofylline Sublingual Tablets Using Sodium Starch Glycolate and Crosscarmellose Sodium as Superdisintegrant

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Abstract
Asthma and COPD (Chronic Obstructive Pulmonary Disease) are the most common life threatening pulmonary disease that requires constant monitoring. Xanthine derivatives are used since a long period of time for treatment of Asthma and COPD. Doxofylline is a new generation xanthine derivative that works by inhibition of phosphodiesterase activities with no cardiovascular side effects that usually seen in case of theophylline and other xanthine derivatives due to decreased affinities towards adenosine A1 and A2 receptors. Doxofylline is an anti-tussive and bronchodilator used for maintenance therapy in patients suffering with asthma and chronic obstructive pulmonary disease (COPD) and is highly metabolised by liver to an extent of 80-90%. Doxofylline is coming under class III of BCS classification and water soluble. Present work studies were carried on the formulation and evaluation of sublingual tablets of Doxofylline using super disintegrant like sodium starch glycolate and crosscarmellose with a view to obtain rapid disintegration when held beneath the tongue, permitting direct absorption of the active ingredient by the oral mucosa and it also by passes fast pass metabolism and improve the bioavailability. Different Precompression and post compression characterization of tablet was carried out and the result satisfied according to the pharmacopoeia specifications. In-vitro release studies were carried out in USP II paddle type dissolution apparatus for different formulations. In-vitro release kinetic studies were carried out for zero order, first order and Higuchi kinetic model. FTIR studies were carried out for pure drug Doxofylline, MCC, PVPK30, SSG, crosscarmellose and for optimised formulation to confirm that there is no interaction between drug and different excipients used in the formulation. DSC studies were carried out to know the thermal stabilities of drug and optimised formulation. Accelerated stability studies were carried out to confirm the stability of dosage forms.

Key words: *Doxofylline, Antiasthmatic, Sublingual tablets, crosscarmellose, sodium starch glycolate*

Introduction

Sublingual tablets are the types of solid dosage form that to be placed under the tongue and produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue. The drug absorbed from stomach goes to mesenteric circulation which connects to stomach via portal vein that are usually metabolised by liver called as first pass metabolism. But the drugs whose absorption takes place through oral cavity avoids first-pass metabolism because in oral cavity the highly vascularised mucosal lining followed by jugular veins and superior vena cava directly links to arterial circulations. The tablets are usually small and flat, compressed lightly to keep them soft and they must dissolve quickly allowing the API to be absorbed quickly. It's designed to dissolve in small quantity of saliva. After the tablet is placed in the mouth below the tongue, the patient should avoid eating, drinking, smoking and possibly talking in order to keep the tablet in place and swallowing of saliva should also be avoided since the saliva may contain dissolved drug. Different formulations such as tablets, films and spray are useful for sublingual administration of drug. [2,3] The task of formulation of sublingual dosage form is very challenging. The challenges are mechanical strength, disintegration time, taste masking, mouth feel, sensitivity to the environmental condition and cost etc. The sublingual tablets are usually prepared by using various superdisintegrant like sodium starch glycolate, different grades of crosscarmellose and different grade of crosspovidone etc for quick and easy disintegration of tablets [1, 3].

Asthma and COPD (Chronic Obstructive Pulmonary Disease) are the most common life threatening pulmonary disease that requires constant

monitoring. Xanthine derivatives are used since a long period of time for treatment of Asthma and COPD. Doxofylline is a new generation xanthine derivative that works by inhibition of phosphodiesterase activities with no cardiovascular side effects that usually seen in case of theophylline and other xanthine derivatives due to decreased affinities towards adenosine A1 and A2 receptors. Doxofylline is chemically designated as 7-(1, 3 dioxolone-2-yl methyl) theophylline. Presence of a dioxolane group in position C-7 differentiates it from theophylline. Doxofylline is an anti-tussive and bronchodilator used for maintenance therapy in patients suffering with asthma and chronic obstructive pulmonary disease (COPD) and is extensively metabolized in liver by demethylation and oxidation to an extent of 80-90% and 50% plasma protein bound Elimination half life ($t_{½}$) is around 6-7 hour and daily dose is 200-400 mg two to three times in a day. Doxofylline is coming under class III of BCS classification and well absorbed orally. It is having solubility of 12 mg/ml in water and having P^{Ka} 9.87[2].

The present studies were carried on the formulation and evaluation of sublingual tablets of Doxofylline using super disintegrant like sodium starch glycolate and crosscarmellose with a view to obtain rapid disintegration when held beneath the tongue, permitting direct absorption of the active ingredient by the oral mucosa and it also by passes fast pass metabolism and improve the bioavailability by reducing the overall daily dose.

Materials and methods

Materials

Doxofylline was procured as a gift sample from Dr. Reddy's Laboratories Hyderabad, India.

The superdisintegrant Sodium Starch Glycolate (SSG) and crosscarmellose sodium were also obtained as a gift sample from Dr. Reddy's laboratories Pvt. Ltd. The diluent Micro crystalline cellulose (Avicel 101) and mannitol were purchased from Otto Manufacturers. PVP K30, Talc and magnesium Stearate were purchased from S.D. fine chemicals Pvt. Ltd' Mumbai, India. All the ingredients were of laboratory grade. The distilled water used in the process of research work was prepared by double distillation process in the laboratory.

Methods

Determination of λmax of pure Doxofylline and preparation of calibration curve :

Primary stock solution of Doxofylline having concentration of 1000µg/ml was prepared using phosphate buffer P^H 6.8. From the primary stock solution after necessary dilution secondary stock solution having concentration of 10µg/ml was prepared using same phosphate buffer P^H 6.8. The prepared secondary stock solution was then scanned by a UV spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at wavelengths ranging from 400nm to 200nm, and the λmax for solution was determined and it was found to be 274 nm. The secondary stock solution was then diluted using same phosphate buffer P^H 6.8 to form a series of concentration of 2, 4, 6, 8, and 10 µg/ml and corresponding absorbance were measured at λmax of 274nm. For obtaining the calibration curve of pure Doxofylline, the measured absorbencies were plotted against corresponding concentrations.

Formulations of Doxofylline sublingual tablets

Sublingual tablets of Doxofylline were prepared by wet granulation method. Accurate quantities of all ingredients were weighed and passed through sieve no #80 before their use in formulations. For each formulation specific and accurate quintile of powder like Doxofylline, MCC, SSG, Cross carmellose, and PVP K30 were blended uniformly and passed through #20. PVP K30 was used as binder. The aggregates formed after addition of binder were initially dried for 5-10 minutes to reduce moisture level and to prevent sticking with sieve. The aggregates were passed through sieve # 44 to get granules. The granules are dried at 40^o C for 20 minutes to reduce moisture content upto 2-5 %. Magnesium stearate and talc were used as lubricants and the required quantities are mixed with dried granules for 2-3 minutes [10]. After lubrication the formulations were evaluated for angle of repose, bulk density, compressibility; and flow properties of granules were predicted prior to compression. The evaluated granules were compressed into tablets on a 10-station rotary punching machine (Saimach Pharmaceutical Pvt. Ltd.) using 8mm concave punches. Each tablet contains 100 mg of Doxofylline. The formulas for different formulations are given in table-1 and same method was followed for all the formulations mentioned in the formulation table [3].

Table 1: Compositions of different excipients used in Doxofylline sublingual tablet formulations F_1-F_{15}

F. No.	Doxofylline (mg)	Avicel 101 (mg)	Mannitol (mg)	SSG (mg)	Cross carmellose (mg)	PVP (mg)	Saccharine (Mg)	Mg. stearate (mg)	Talc (mg)	Total wt. (mg)
F_1	100	52	20	2	-	20	1	3	2	200
F_2	100	50	20	4	-	20	1	3	2	200
F_3	100	48	20	6	-	20	1	3	2	200
F_4	100	46	20	8	-	20	1	3	2	200
F_5	100	44	20	10	-	20	1	3	2	200
F_6	100	52	20	-	2	20	1	3	2	200
F_7	100	50	20	-	4	20	1	3	2	200
F_8	100	48	20	-	6	20	1	3	2	200
F_9	100	46	20	-	8	20	1	3	2	200
F_{10}	100	44	20	-	10	20	1	3	2	200
F_{11}	100	50	20	2	2	20	1	3	2	200
F_{12}	100	48	20	3	3	20	1	3	2	200
F_{13}	100	46	20	4	4	20	1	3	2	200
F_{14}	100	48	20	4	2	20	1	3	2	200
F_{15}	100	48	20	2	4	20	1	3	2	200

Differential Scanning Calorimetric (DSC) analysis:

The DSC analysis of Doxofylline and physical mixture of drug with excipients used for formulations were carried out using a Shimadzu DSC 60, Japan; to evaluate any possible polymer drug thermal interaction. Exactly weighed 5 to 6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10^o C/min over a temperature range of 40 to 300^{o}C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min [10, 11].

Evaluation of pre-compression parameters of Doxofylline sublingual granules of all formulations

Angle of Repose (θ):

This is the maximum angle possible between the surface of a pile of granules and the horizontal plane. The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \theta = h/r$$

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

Where, θ = angle of repose
h = height of the heap
r = radius of the heap

According to the specifications the angle of repose value less than 25^0 indicates excellent flow whereas angle between25^0-30^0 indicates good flow. The angle between 30^0-40^0 indicates passable flow and angle greater than 40^0 indicates very poor flow.

Bulk density:

Both the loose bulk density (LBD) and tapped bulk density (TBD) of prepared Doxofylline sublingual granules of all the formulations were determined. The quantity of 2 gm of granules from each formula, previously lightly shaken to break any agglomerates formed; were introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface form the height of 2.5 cm at second interval. The tapings were continued until no further changes in volume were noted. LBD and TBD of prepared granules were calculated using the following formulas. The results of each formulation were given in table-2.

$$LBD = \frac{weight\ of\ the\ granule}{volume\ of\ the\ packing}$$

$$TBD = \frac{weight\ of\ the\ granule}{tapped\ volume\ of\ the\ packing}$$

Compressibility Index (Carr's index):

The flow ability of granules can be evaluated by comparing the loose bulk density (LBD) and tapped bulk density (TBD) of powder and the rate at which it packed down.

Compressibility index (Carr's index) of prepared Doxofylline sublingual granules were calculated by following formula

$$Carr's\ index\ (\%) = \frac{TBD-LBD}{TBD} \times 100$$

According to the specification the Carr's index values between 5-15 indicates excellent flow where as between 12-16 indicates good flow. Values between 18-21 indicate fare-passable where as between 23-25 indicates poor. Between 33-38 indicates very poor and greater than 40 indicates extremely poor.

Hausner's ratio:

The Hausner's ratios of prepared Doxofylline sublingual granules were determined by following formula. The results of each formulation were given in table-2.

$$Hausner's\ ratio = \frac{TBD}{LBD}$$

According to specifications values less than 1.25 indicate good flow (=20% of Carr's index), where as greater than 1.25 indicates poor flow (=33% of Carr's index). Between 1.25 and 1.5, added glidant normally improves flow.

Evaluation of postcompression parameters of Doxofylline sublingual tablets of all formulations

Thickness

Ten Doxofylline sublingual tablets from each formulation were randomly selected and used for thickness determination. Thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo dial Thickness Gauge, Mitutoyo,Japan) and the results were expressed as mean values of ten readings, with standard deviations. According to specification tablet thickness should be controlled within a ± 5% variation of standard value.

Tablet Hardness

All the formulations of Doxofylline sublingual tablets hardness were measured by using Monsanto hardness tester. From each formulation the crushing strength of ten sublingual tablets with known weights were recorded in kg/cm^2 and average were calculated and presented with standard deviation. According to specifications of USP hardness values of 3-3.5 Kg for sublingual tablet is considered as acceptable limit.

Friability

Previously weighed 10 Doxofylline sublingual tablets from each batch were taken in Roche friabilator (Roche friabilator, Secor India, Delhi, India). After100 revolutions of friabilator tablets were recovered. The tablets were then made free from dust and the total remaining weight was recorded. Friability was calculated from the following formula.

% F = ($W_0 - W_1$)/ $W_0 \times 100$, where W_0 and W_1 were the initial and final weight of the tablets before and after friability test. For compress tablet that lose less than 0.1 to 0.5 % and maximum upto 1% of the tablet weigh are consider acceptable.

Weight variation test

All formulated Doxofylline sublingual tablets were evaluated for weight variation as per USP monograph. Twenty tablets were weighed collectively and individually using an electronic balance. The average weight was calculated and percent variation of each tablet was calculated. According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130mg or less is 10% whereas for average weight between 130-324mg is 7.5% and for average weight more than 324mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more than 15%.

Content uniformity

Twenty Doxofylline sublingual tablets were taken and triturated to form powder and powder equivalent to one tablet was taken and dissolved in 100 ml of phosphate buffer P^H 6.8 and heated at 37 ^{0}C for 15-20 minutes with stirring. The solution was filtered, suitably diluted and the Doxofylline content was measured by using UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 274 nm. Each measurement was carried out in triplicate and the average drug content in the Doxofylline sublingual tablets was calculated.

***In-vitro* disintegration time (D_t)**

According to USP (United States Pharmacopoeia) disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (<2 min) for sublingual dosage form. The test was carried out using tablet disintegration apparatus (model EI D-16, Electrolab, Mumbai, India). *In-vitro* disintegration test was carried out using a modified disintegration method (n = 6) using disintegration tester maintained at 37°C ± 0.5°C in phosphate buffer P^H 6.8. The tablets were kept in the basket and noted the time taken for the tablet to disintegrate completely into smaller particles [14].

Wetting time and water absorption ratio

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 6.5 cm containing 10 ml of phosphate buffer P^H 6.8 containing methylene

blue (0.1% w/v). A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for the dye to reach the upper surface of the tablet was recorded as wetting time. Measurements were carried out in triplicate and standard deviations were also determined.
Water absorption ratio(R), can be estimated by simple procedure include weighing (W_b) of the tablet prior to the placement on the Petri dish, then after recording the wetting time. The wetted tablet was removed and reweighed (W_a), the water absorption ratio was determined according to the following equation:
$R = 100 \times (W_a - W_b)/ W_b$
Where W_b and W_a were tablet weights before and after water absorption, respectively [15].

***In-vitro* drug release study**

Dissolution study was conducted for all the formulations using USP dissolution rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India.). A total volume of 900 ml of phosphate buffer P^H 6.8 was taken as dissolution medium, which was maintain at 37°C ± 0.5°C at 50 rpm. 5ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 5 min intervals and filtered by whatman filter paper. Samples were analyzed spectrophotometrically at 274 nm for determination of Doxofylline that were released from sublingual tablets [16,17].

Characterization of the *in vitro* drug release profile

The rate and mechanism of release of Doxofylline from prepared Sublingual tablets were analyzed by fitting the dissolution data into following exponential equations.

Zero order release equation:

$Q = K_0 t$
Where Q is the amount of drug released at time t and K_0 is the zero order release rate constant.

The first order equation:

$\ln (100 - Q) = \ln 100 - K_1 t$
Where, K_1 is the first order release rate constant.
The dissolution data was fitted to the Higuchi's equation:

$Q = K_2 t^{1/2}$
Where, K_2 is the diffusion rate constant.
The dissolution data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behaviour from polymeric systems:

$\text{Log } (Mt/M\infty) = \log K + n \log t$
Where Mt is the amount of drug released at time *t*, $M\infty$ is the amount of drug release after infinite time, K is a release rate constant and n is the diffusion exponent indicative of the mechanism of drug release.
For matrix tablets, if the exponent $n < 0.5$, then the drug release mechanism is quasi-fickian diffusion (If $n = 0.5$ then fickian diffusion and if the value is $0.5 < n < 1$, then it is anomalous diffusion coupled with erosion. An exponent value of 1 is indicative of Case-II Transport or typical zero-order and $n > 1$ non-fickian super Case II). The diffusion exponent was based on Korsmeyer-Peppas equation. [19]

Stability studies of optimised formulation (F_{14})
The stability studies of optimised formulation (F_{14}) were carried out according to ICH guidelines. The optimized formulation was subjected to stability study at 40 °C ± 2 °C/ 75% ± 5% RH for 90 days. After that period the product was evaluated for friability, hardness, weight variation, thickness, drug content and in vitro release study [20].

Result and Discussion

Compatibility studies by FTIR and DSC:

The FTIR spectra of pure drug Doxofylline, MCC, mannitol, cross carmellose, SSG, PVPK30, magnesium Stearate, talc and physical mixture (optimised formulation:F_{14}) of drug with all excipients used were shown in fig-1. By comparing the spectra of Doxofylline, MCC, cross carmellose, SSG, magnesium Stearate, talc and optimised formulation (F_{14}), the sharp peaks that appear in spectra of Doxofylline at~ 3110 cm^{-1} also appears in physical mixture (drug and excipients) at~ 2916 cm^{-1} and sharp peak that appears in spectra of MCC at~ 3418 cm^{-1} also appear in spectra of physical mixture (drug and excipients) at~ 3399 cm^{-1}. The broad peak between~ 3500 $cm^{-1}$to ~ 3000 cm^{-1} appears both in MCC, SSG, cross carmellose, PVPK30, magnesium Stearate and physical mixture (drug and excipients). The characteristic IR absorption peaks of Doxofylline at ~ 1700 cm^{-1} (C=O stretch), at ~ 1656 cm^{-1} (C=C stretch), at ~ 1547 cm^{-1} (C=N stretch), at ~ 1477 cm^{-1} (C-H bend) and at ~ 1190 cm^{-1} (C-N vibration) were also present in the physical mixture (drug and excipients) with no shifting in the major peaks and there was no additional peaks formed in the physical mixture (drug and excipients), that indicate there were no interaction occurred between the Doxofylline and excipients used in the preparation of different sublingual formulations.

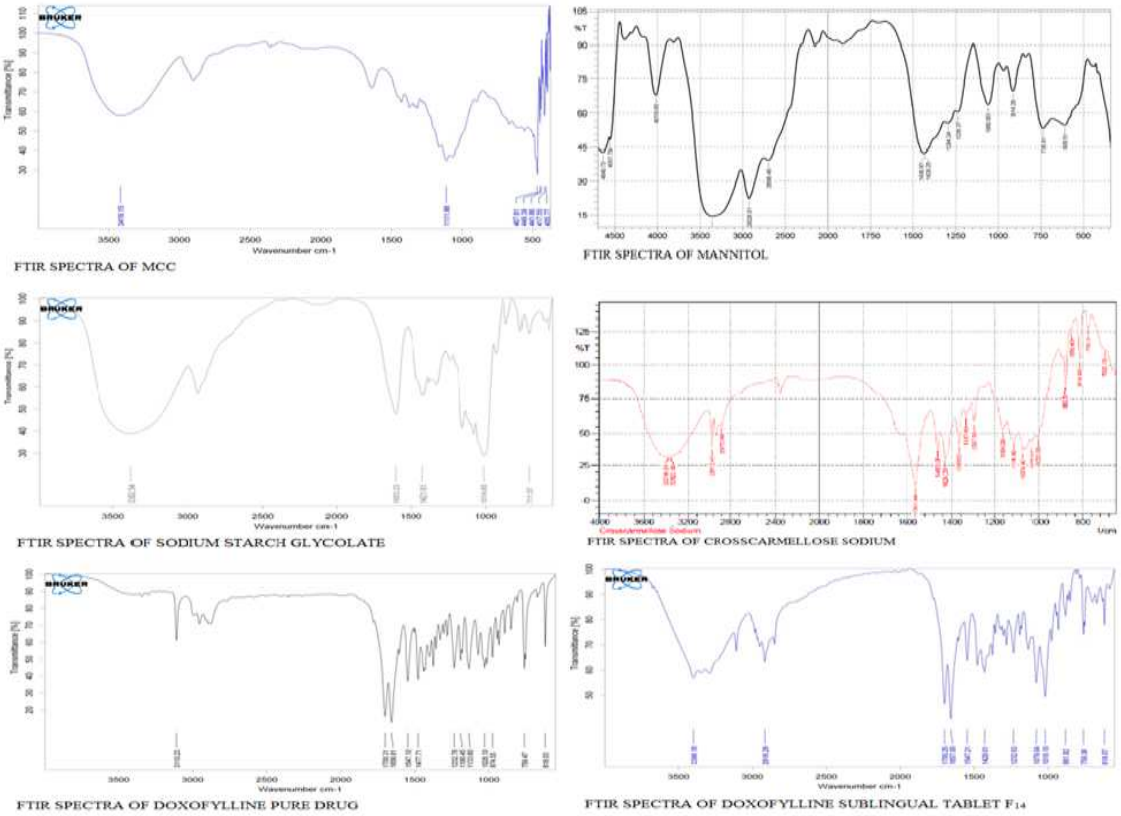

Fig 1: FTIR studies of pure drug Doxofylline, exipents(MCC, Manitol, SSG, CCS) and optimised formulation F14

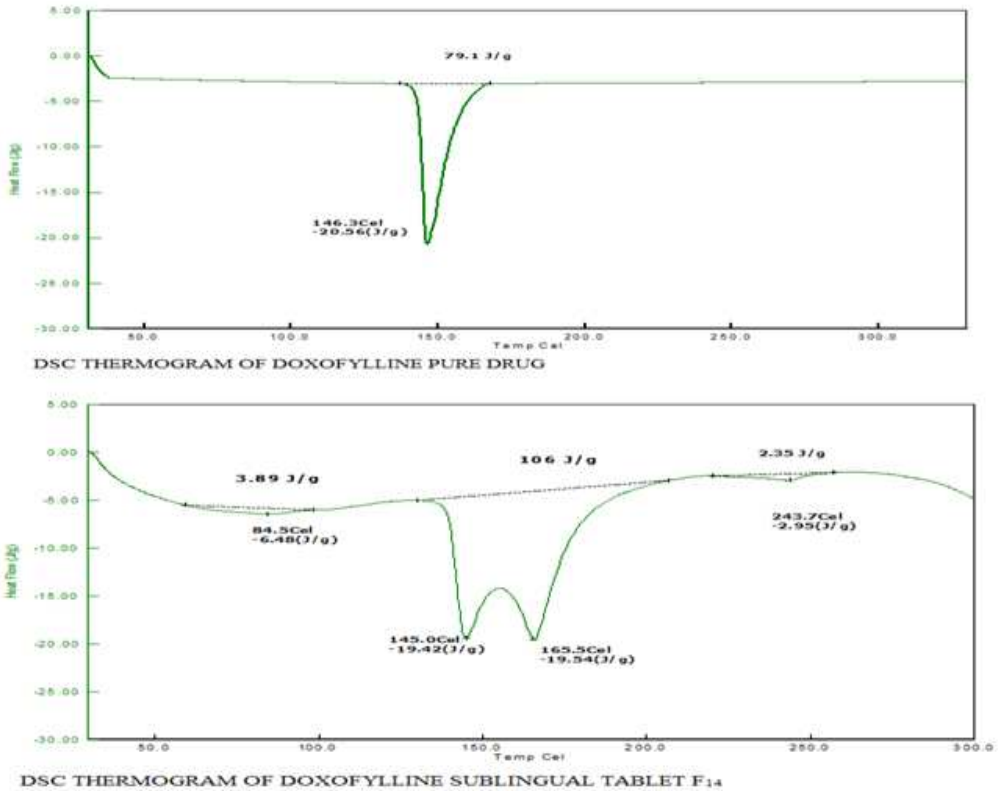

Fig 2: DSC studies of pure drug Doxofylline and optimised formulation F14

DSC thermogram of pure drug Doxofylline and physical mixture (drug and excipients) were obtained and it was observed that the endothermic peak appeared at 146 ^{0}C and 165 ^{0}C respectively which indicate that the physical mixture (drug and excipients) is thermodynamically stable because the formulation required more heat than pure drug due to presence of various excipients like MCC, mannitol, cross carmellose, SSG, PVPK30, magnesium Stearate, talc. The DSC data are given in fig-2.

Precompression parameters studies:

The granules of Doxofylline sublingual tablets were prepared by wet granulation method which is a conventional method and most advantageous than others. A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. Physical properties of granules such as specific surface area, shape, hardness and size can significantly affect rate of dissolution of drugs and hence overall bioavailability of drug in heterogeneous formulation. The result of angle of repose of granules after mixing with magnesium stearate and talc were less than 25^o for all formulations that indicates excellent flow properties of granules. Compressibility index is also less than 16% for most of the formulations except F_2, F_5, F_6, F_{12} and F_{13} which indicates good to excellent flow properties of granules. Bulk density of granules with formulations F_8 and F_4 are higher than others which indicate presence of more fines in the formulations. The percentage porosity values of the granules indicating that the packing of the granules may range from close to loose packing. The Hausner's ratio values lies below 1.25 for all formulations which also satisfy with good flow properties of granules according to standard specifications. The results of precompression parameters were shown in table-2.

Post compression parameters studies

The physical properties like average hardness, average weight variation, average friability, thickness of tablets were studied. The physicochemical characterizations of different batches of Doxofylline sublingual tablets are given in Table-3.The thickness of the tablets were ranged between 4.79±0.14 to 4.90±0.16 mm. All the batches showed uniform thickness. Weight variations for different formulations were found to be 198±1.72 to 202±1.46mg. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement. The hardness of all the Doxofylline sublingual tablets formulations were ranged from 1.02±0.2 to 2.97±0.5 kg/cm^2. By increasing the concentration of superdisintegrant concentration the hardness usually decreased that noticed in case of formulation F_5, F_{10} and F_{13}. The percentage friability of all the formulations were ranged from 0.49±0.04% to 0.98±0.06% and also the % friability were found more by increased concentration of superdisintegrant concentration. In the present study, the percentage friability for all for formulations was within the prescribed limits. The percentages of drug content for F_1 to F_{15} were found to be in between 98.21±1.2 to 101.22±1.4 of Doxofylline sublingual tablet formulations which were within the acceptable limits. Disintegration time were determined for all the formulations and it was found that by increasing concentration of superdisintegrant disintegration time decreases; but increase in concentration above 3% the hardness value didn't fall in the acceptable range. The wetting time of all the formulations were found between 20±0.62 to 98±0.65. For the case of wetting time by increasing the concentration of superdisintegrant the wetting time decreases those were noticed in case of formulations of F_5, F_9 and F_{10}. Between SSG and cross carmellose the later having less wetting time than former at equal concentrations. The water absorption ratio of formulations F_1 to F_{15} was found in the range of 12.4±0.34 to 30.42±0.28. By increasing the concentration of superdisintegrant the water absorption ratio increases that might be due to increase in the porosity of the formulation with increase in superdisintegrant concentration. The results of postcompression parameters were shown in table-3.

The *in-vitro* drug release characteristics of Doxofylline sublingual tablets were studied in phosphate buffer P^H 6.8 dissolution medium for a period of 20 to 25 minutes using USP type-II paddle type dissolution apparatus. The rate of dissolution increased by increasing the concentration of superdisintegrant but above 3% as the hardness decreases it was considered as the optimum concentration. When both the superdisintegrants were used in combination in total concentration of 3% it shows some better dissolution profile and release almost all the drug within 10 minutes. Formulation F_{14} having superdisintegrant concentration of 3% (2% cross carmellose and 1% SSG) release the drug within 10 minutes. Combination of MCC and mannitol worked good as diluents so it was used in all the formulations. The dissolution profile of all the formulations (F_1 to F_{15}) were shown in fig-3.

Table 2: Evaluation of precompression parameters of Doxofylline sublingual tablet granules for formulations F_1- F_{15}

F. No.	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose	Carr's index	Hausner's ratio
F_1	0.438±0.02	0.524±0.05	23.48±0.16	16.41	1.20
F_2	0.492±0.06	0.593±0.06	22.59±0.14	17.03	1.21
F_3	0.468±0.03	0.508±0.04	22.98±0.17	7.87	1.08
F_4	0.505±0.04	0.583±0.08	23.67±0.14	13.55	1.16
F_5	0.408±0.06	0.496±0.07	24.87±0.12	17.74	1.22
F_6	0.396±0.05	0.492±0.04	23.68±0.16	19.51	1.24
F_7	0.487±0.02	0.526±0.06	24.59±0.18	7.38	1.08
F_8	0.542±0.07	0.598±0.04	23.61±0.14	9.36	1.10
F_9	0.473±0.03	0.529±0.06	24.05±0.15	10.58	1.12
F_{10}	0.479±0.04	0.521±0.05	23.13±0.17	8.06	1.09
F_{11}	0.488±0.05	0.563±0.09	21.23±0.14	15.36	1.15
F_{12}	0.439±0.06	0.531±0.02	20.19±0.20	20.95	1.21
F_{13}	0.481±0.06	0.568±0.04	24.34±0.15	18.08	1.18
F_{14}	0.465±0.07	0.549±0.06	22.32±0.12	18.06	1.18
F_{15}	0.473±0.08	0.523±0.09	21.56±0.18	10.57	1.11

All values are expressed as average± SD; (n=3)

Table 3: Evaluation of post-compression parameters of Doxofylline sublingual tablets formulation F_1- F_{15}

F. No.	Average hardness (kg/cm^2)	Average Weight Variation (mg)	Average friability (% w/w)	Average thickness (mm)	Drug content (%)	D_t (Sec)	Wetting time (Sec)	Water absorption ratio
F_1	2.97±0.5	202±1.23	0.49±0.04	4.89±0.15	98.74±1.5	186±1.04	98±0.65	12.4±0.34
F_2	2.54±0.6	200±1.64	0.51±0.05	4.90±0.16	101.22±1.4	168±0.93	74±0.43	13.15±0.28
F_3	2.09±0.7	201±2.14	0.52±0.06	4.89±0.18	100.29±1.2	136±0.85	61±0.56	16.52±0.36
F_4	1.35±0.8	199±1.20	0.85±0.04	4.82±0.24	99.46±1.6	114±0.89	48±0.38	19.45±0.38
F_5	1.02±0.2	198±1.72	0.91±0.08	4.84±0.26	99.74±1.2	98±0.63	42±0.72	25.24±0.41
F_6	2.81±0.7	200±1.68	0.48±0.04	4.82±0.16	100.45±1.4	174±0.82	54±0.49	15.33±0.45
F_7	2.50±0.8	201±2.18	0.53±0.05	4.84±0.19	99.14±1.1	142±0.65	38±0.56	19.21±0.39
F_8	2.21±0.4	202±1.44	0.78±0.06	4.83±0.10	100.02±1.4	126±0.84	32±0.82	21.28±0.42
F_9	1.28±0.9	201±1.47	0.95±0.03	4.85±0.20	98.21±1.2	116±0.72	22±0.75	26.27±0.37
F_{10}	1.07±0.5	199±1.36	0.98±0.06	4.84±0.28	99.29±1.4	92±0.64	20±0.62	29.16±0.44
F_{11}	2.32±0.6	200±1.28	0.59±0.04	4.81±0.16	98.62±1.6	126±0.68	68±0.58	14.19±0.41
F_{12}	2.11±0.8	202±1.46	0.62±0.05	4.79±0.14	99.22±1.3	118±0.56	44±0.62	22.44±0.40
F_{13}	1.42±0.7	199±1.72	0.92±0.06	4.84±0.24	98.42±1.6	97±0.84	34±0.64	29.71±0.43
F_{14}	2.13±0.6	200±1.34	0.82±0.04	4.85±0.28	99.19±1.5	78±0.67	46±0.74	30.42±0.28
F_{15}	2.15±0.5	199±1.56	0.74±0.06	4.80±0.25	99.45±1.8	86±0.55	38±0.81	28.54±0.32

All values are expressed as average± SD; (n=3)

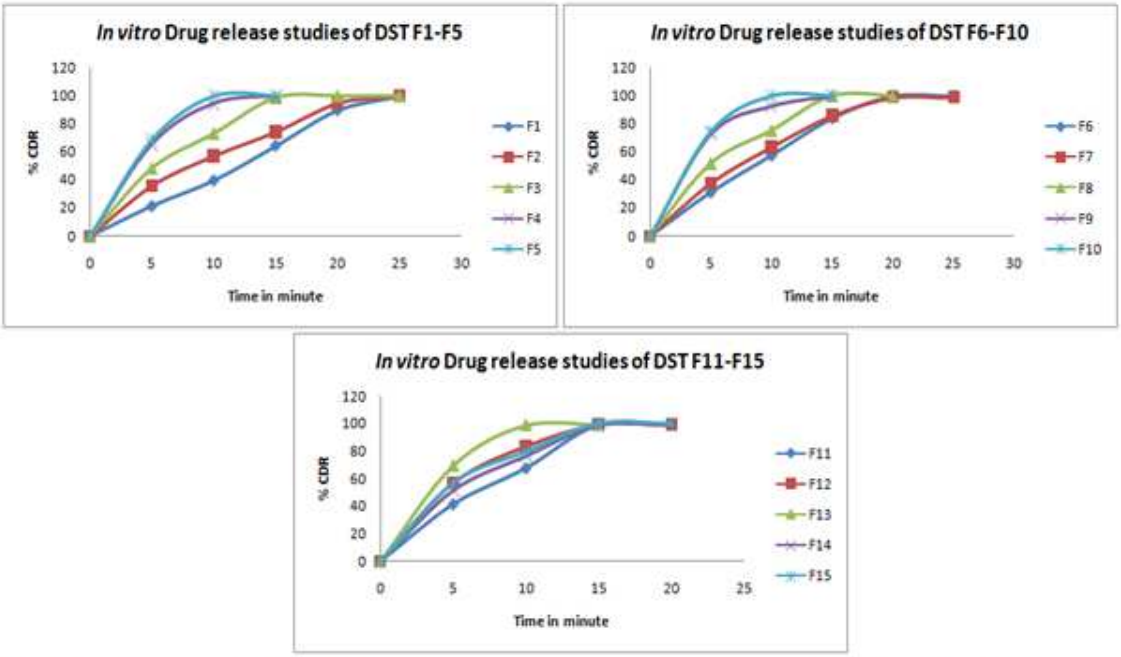

Fig 3: In vitro release studies of Doxofylline sublingual tablet (DST) of formulations F1-F15

The *in vitro* dissolution data of Doxofylline sublingual tablets were fitted in different kinetic models viz. zero order, first order, Higuchi and Korse Meyer- Peppas equation and the graphs were plotted (Fig 3). The zero-order plots were found to be fairly linear as indicated by their high regression values for F_{14} formulation. The release exponent 'n' for optimised formulation F_{14} was found to be 0.59 ($0.5 < n < 1$), which appears to indicate a coupling of the diffusion and erosion mechanism so-called anomalous diffusion. So in present study *in vitro* drug release kinetic of Doxofylline sublingual tablet followed zero order release kinetic model and the drug release mechanism was said to be anomalous diffusion coupled with erosion.

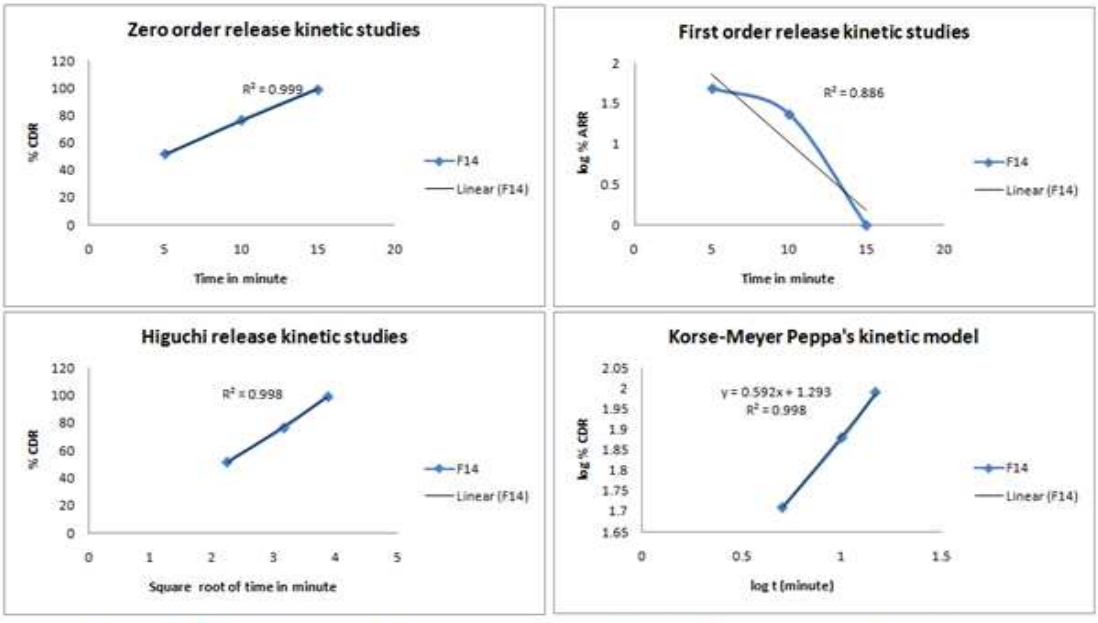

Fig 4 *In vitro* release kinetic studies of Doxofylline sublingual tablet optimised formulation(F14)

The optimised formulation F_{14} of Doxofylline sublingual tablets was selected for the accelerated stability studies. The results of in-vitro release profile of optimised formulation at different time interval for accelerated stability conditions were shown in fig-5. The Doxofylline sublingual tablets did not show any significant change in physicochemical parameters and *in vitro* drug release characteristics. Thus, it was found that the sublingual tablets of Doxofylline (F_{14}) were stable under short term storage conditions for at least 3 months.

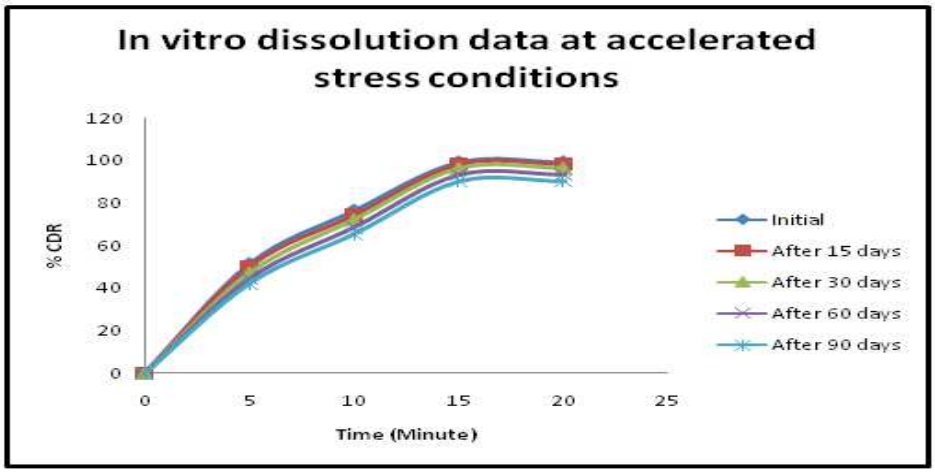

Fig 5: In vitro dissolution data of optimised formulation (F14) at accelerated stress conditions

Conclusion

In the present work Doxofylline sublingual tablets were successfully developed. The major challenge in this work was to study the effect of sodium starch glycolate and cross carmellose sodium on *in vitro* release rate of sublingual tablet of Doxofylline. The sublingual drug delivery system was a promising approach to achieve increase in bioavailability of drug like Doxofylline that are highly metabolised. FTIR studies revelled that there is no chemical interaction between drug and excipients. DSC studies proved that no thermal interaction between the drug Doxofylline and excipients used in the present studies. FTIR and DSC studies revealed that the drug and excipients were compatible with each other and formulation is thermally stable. Wet granulation methods were adopted for the preparation of Doxofylline sublingual granules and the evaluation results of all the precompression parameters were satisfied the acceptance criteria. All the postcompression parameters like average thickness, hardness, friability, weight variation and disintegration also fall within acceptable limit. Mannitol and MCC were used both as diluents for all the formulations for better drug release. Formulation F_{14} containing 1% of SSG and 2% of cross carmellose showed complete drug release within 15 minute (99%) emerging as optimised formulation and using both the superdisintegrant in combination it gives better drug release profile. By increase in superdisintegrant concentration the drug release profile became faster but the hardness and friability of the formulation were severely affected. Kinetic of *in vitro* drug release of optimized formulation F_{14} found to be zero order having drug release mechanism as anomalous diffusion coupled with erosion. The stability studies were carried out according to ICH guideline and selected F_{14} formulation were stable at 40°C/75% RH up to 3 months with a little change in physicochemical characteristics of the formulations. Thus from the results of the current study clearly indicate, a promising potential of the Doxofylline sublingual system as an alternative to the conventional dosage form because it bypass the fast pass metabolism and improve the bioavailability of the drug and over all daily dose can be reduced. However, further clinical studies are needed to assess the utility of this system for patients suffering from asthma and COPD.

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