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Preparation and evaluation of pentoxifylline loaded chewable tablet for the treatment of peripheral vascular diseases

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ABSTRACT

Pentoxifylline, an analogue of theophylline and phosphodiestrase inhibitor is used in the treatment of peripheral vascular diseases. The objective of present investigation was to formulate and in-vitro characterize pentoxifylline loaded chewable tablets for the treatment of peripheral vascular disease with varying concentration of sodium starch glycolate (SSG) as super-disintegrent. The pentoxiphyline loaded chewable tablets were prepared by using wet granulation technique. Lactose and mannitol were used as diluents with different concentration of sodium starch glycolate (SSG) as super-disintegrate The in-vitro drug release profile was carried out in phosphate buffer phosphate buffer saline (PBS pH 6.8) at 37±0.1ºC using USP paddle type II. Prepared granules were subjected to precompression studies like angle of repose and compressibility indices. The compressed formulations were then evaluated for appearance, thickness, weight variation, hardness, friability, drug content uniformity, wetting time and disintegration time and in-vitro drug release profile. The results of all evaluation parameters were within acceptable limits. From the disintegration studies, it was observed that the formulation containing 4.0% w/w of sodium starch glycolate showed minimum disintegration time than other formulations. The optimised formulation showed 97.82% in-vitro drug release in 30 minutes.A significant difference was observed in in-vitro drug release due to varying concentration of superdisintegrant as well as diluents. Thus, it can be concluded that Pentoxifylline loaded chewable tablet can be a potential dosage form for the therapy of peripheral vascular diseases.

Keywords: Pentoxifylline, Peripheral vascular diseases, Chewable tablet, Sodium starch glycolate (SSG).

INTRODUCTION

Oral route has been employed as major route for drug delivery for chronic treatment of many diseases. It is most preferred route by medical practitioners and manufacturers due to highest acceptability of patients. It is most easy and convenient route of administration of drug; it is safest route as allergic reaction of the drug (toxicity) is delayed [1]. It is well established that the active ingredient in a solid dosage form must undergo successive rate processes, before it is available for absorption from the gastrointestinal tract. These processes are disintegration, release of the drug, and dissolution of the drug in an aqueous environment.Chewable tablets are the tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing. Successfully tablet formulation development involves the careful selection of ingredients in order to manufacture a robust solid dosage form [2].However, pediatric, geriatric and bedridden patient shows inconvenience swallowing conventional tablets or capsules due to difficulties in swallowing with lesser amounts of water with the medication, unable to tolerate the taste of many drugs when formulated as liquid dosage forms, resulting in poor patient compliance.Chewable tablets are also used in the administration of antacids and antiflatulents (to remove excessive amount of gas from GIT). There are many advantages of chewable tablets like, providing quick and complete disintegration of the tablet and thus produce rapid drug effect after swallowing and dissolution [3].

Pentoxifylline is a tri-substituted xanthine derivative designated chemically as 1-(5-oxohexyl)3,7 dimethylxanthine that, unlike theophylline, is a hemorrheologic agent, i.e. an agent that affects blood viscosity. Pentoxifylline is a methyl xanthine derivative that inhibits phosphodiestrase and affects blood rheology. It improves blood flow by increasing erythrocyte and leukocyte flexibility[4]. It is soluble in water, ethanol and sparingly soluble in toluene. Plasma half-lives of pentoxifylline and its metabolites are 0.4 to 0.8 hours and 1 to 1.6 hours respectively.Due to short half-life, daily large doses have to be given and frequent dosing is required [5].

MATERIALS AND METHODS

Materials

Pentoxifylline was received as a gift sample from Shreya Life Sciences, Aurangabad, M.S, India. All other ingredients such as sodium starch glycolate, acacia, lactose, mannitol, magnesium stearate, talc and strawberry flavour were purchased from Central Drug House (CDH) New Delhi, India. All ingredients used were of analytical grade.

Method

Chewable tablets of pentoxifylline were prepared by wet granulation technique using 1% starch solution as a binder lactose, mannitol, aspartame, strawberry flavor were used as diluents while SSG was used as superdisintegrant. All excipients were properly weighed and mixed together except glidant and lubricant and made dough. Then passed through sieve no. 16 and granules were dried at 50-60 ºC for 30 minute in hot air oven. After drying talc and magnesium stearate were added and tablets were compressed by using single rotatory compression machine [6].The formulation table of pentoxifylline loaded chewable tablet was shown in table 1.

Table 1: Formulation table of pentoxifylline loaded chewable tablet

INGREDIENTS (mg)	F1	F2	F3	F4	F5
Pentoxifylline	50	50	50	50	50
SSG	4	8	12	16	20
Lactose	-	328	-	320	-
Mannitol	330	-	324	-	316
Aspartame	4	4	4	4	4
Strawberry flavour	2	2	2	2	2
Magnesium stearate	5	5	5	5	5
Talc	5	5	5	5	5

EVALUATION OF PENTOXIFYLLINE LOADED CHEWABLE TABLETS

Pre-compression studies of pentoxifylline granules

Preformulation study is the first step in drug development. All studies which are performed prior to the development of dosage form to reduce error and gave a remunerative data to carry out dosage form development. Following pre-compressional parameters were studied like angle of repose, bulk density, tapped density, compressibility indices etc.

Angle of repose

It is defined as the angle of heap to the horizontal plane. Angle of repose was determined by using fixed funnel method. Approximately 1g of granules was transferred to the funnel keeping the orifice of the funnel blocked by thumb. When powder was cleared from funnel the angle of repose was measured [7].

Angle of repose (θ) = $\tan^{-1}$ h/r

Bulk density

It is the ratio of bulk mass of powder to the bulk volume. It is calculated by this formula-

Bulk density = weight of granules in bulk/Bulk volume

Tapped density

It is the ratio of the weight of blend to the minimum volume occupied in measuring cylinder (i.e. tapped volume) by granules. Measuring cylinder containing the porous mass of granules was tapped for fixed time and it was determined by tapped density apparatus [8].

Tapped density = Weight of granules / Tapped volume

Compressibility Indices

a. Carr's index

Based on the apparent bulk density and the tapped density, the percentage compressibility of the powder mixture was determined by the following formula.

Carr's index = Tapped density-Bulk density × 100/ Tapped Density

b. Hausner's ratio

It is an indirect index of ease of measuring of granules flow. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25) [4, 9].

Hausner's ratio = Tapped density/ Bulk density

Post-compression studies of prepared pentoxifylline loaded chewable tablets

The chewable tablets were evaluated for appearance, thickness, weight variation, hardness and friability. In vitro drug release profile carried out by dissolution apparatus and mechanism of drug release studied through various release kinetics equations. All the evaluation parameters of all formulations are given in Table 2.

Physical Appearance

The general appearance and urbanity of tablet was studied visually. The tablet was round in shape, unstained in color with smooth texture.

Thickness

The tablet thickness was calculated by Vernier calipers. Tablet was put in between two jaws vertically and thickness was measured. 6 tablets were used for this test. Thickness of tablet was expressed in millimetre (mm).

Weight variation

The weight of 20 tablets was measured and average weight was calculated. The individual weight of each tablet was measured to check out variation. Weight variation was determined by comparison of individual tablet weight with average weight [2, 10].

Hardness

The tablet hardness was determined by Monsanto hardness tester. The tablet was fitted lengthwise between plunger and force applied. The pressure at which tablet got crushed was measured. It is measured in Kg/cm^2. 6 tablets were used for this study.

Friability

Friability of tablets was measured by Roche friability apparatus. Pre-weighed six tablets were kept in friability apparatus which provided combined effects of shock and abrasion from height of six inches with each rotation, at 25 rpm speed and operated for 100 revolutions. Tablets were dusted and re-weighed [11].

Disintegration time: This test was performed on 6 tablets. For disintegration time, one tablet was placed in the centre of the Petridish (internal diameter 10 cm) containing 10 ml of water and the time taken by the tablet to disintegrate completely was noted.

Wetting time

Five circular tissue papers were placed in a petridish of 10 cm diameter. Ten millilitres of water containing 0.5% eosin, a water-soluble dye, was added to the petridish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petridish at 25°C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicate of six. Wetting time was recorded using a stopwatch [11, 12].

Drug content uniformity

The formulated tablets of pentoxifylline were weighed and crushed. Powder equivalent to 50mg of pentoxifylline was weighed and shaken with 10ml of water in 100ml of volumetric flask and filtered. The aliquot of filtrate was taken and its volume was made up to 100ml with water and absorbance was taken at 275nm by using UV spectrophotometer (UV- 1601, Shimadzu, Japan). The drug content was determined by using UV standard curve of pentoxifylline [13].

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

In vitro studies were carried out using USP type II (paddle type) apparatus (Lab India Dissolution apparatus D5 8000). Dissolution medium was 900 ml phosphate buffer saline (PBS pH 6.8) with paddle rotation at 100 rpm. Temperature was maintained at 37±1°C. Aliquots of 5 ml PBS having released drug were withdrawn after each hour and equivalent amount of fresh buffer maintained at same temperature was replaced to maintain sink conditions. The samples were analysed for pentoxifylline content at 273 nm by using UV-spectroscopy and calculated the drug release using calibration curve of pentoxifylline [6, 13].

***In- vitro* drug release kinetics**

Mechanism of drug release from the chewable tablets can be studied using different mathematical expressions. The kinetic drug-release data was analysed according to zero order, first order, Higuchi square root, Kosmeyer-Peppas equation. The appropriate equation was chosen on the basis of best fit line and its equation given as:

Zero order kinetics: This represents cumulative amount of drug release vs time.

$QT=K_OT$

Where Ko is the zero order rate constant (concentration/time), T is the time (h), and Q represents the amount of drug release in time T, plot obtained from concentration *vs* time would yield a straight line with slope equal to Ko and intercept at the origin of axis [14].

First order kinetics: This represents cumulative percentage of drug release *vs* time.

Log Q = Log Qo– kt/2.303

Where Qo represents the initial concentration of drug, k is the first-order rate constant, and t is time.

Higuchi kinetics: This represents cumulative percent drug release *vs* square root of time.

$Q = kt^{1/2}$

Where k is the rate constant and t is time in h.

Korsmeyer and Peppas model: represents log cumulative percent drug release *vs* log of time.

$Mt / M\infty = Kt^n$

Where K is the constant incorporating structural and geometric characteristic of the device, Mt and M∞ are absolute cumulative amount of drug released at time t and infinity, respectively and n is the diffusional exponent indicative of the release mechanism [1, 14].

Release of drug depends on the value of exponent (n):

If n = 1<0.5, it indicates Quasi Fickian Diffusion.

If n = 0.5, it indicates Fickian Diffusion.

If n= 0.5<n<1, it indicates Anomalous (non-Fickian) Diffusion.

If n= 1.0, it indicates non Fickian (case II): Zero order.

If n> 1.0, Non Fickian super case II [15].

RESULTS

The result related to various measured parameters in terms of pre and post compressional studies of pentoxifylline loaded chewable tablet are given in table 2 % 3. The pre compressional studies of pentoxifylline loaded chewable table was shown in table 2. The bulk density and tapped density of pentoxifylline loaded granules were found in the range of 0.381 to 0.572 g/ml and 0.441 to 0.652 g/ml. The parameters studies like angle of repose, hausner's ratio

and Carr's index which showed the flow property were found to be in the range of 24.01 to 28.08, 1.12 to 1.17 and 12.62 to 14.01 respectively.

Table 2:Pre-compression evaluation parameters of pentoxifylline loaded granules

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (˚)
F1	0.540	0.615	13.01	1.13	25.78
F2	0.401	0.501	14.01	1.14	24.01
F3	0.468	0.551	12.89	1.12	28.08
F4	0.381	0.441	12.79	1.17	26.06
F5	0.570	0.662	12.62	1.15	25.55

The post compressional studies of pentoxifylline loaded chewable tablet was shown in table 2. The weight of Pentoxifylline loaded chewable tablet was found to be in the range of 400±2.0 to 400±3.2 mg. Diameter and thickness were observed as 12±0.01 and 3±0.01. The % friability of various formulations was found to be in between 0.35±0.21 to 0.88±0.11. The hardness of tablet was found to be 3.0±0.012 to 4.2±0.21 kg/cm2. The wetting time and disintegration time of pentoxifylline loaded chewable tablet were observed in the range of 18±0.005 to 76±0.022 and 30±0.21 to 80±0.43 second respectively. The in vitro drug release that was performed for sodium starch glycolate as superdisintegrant containing formulations was in figure 2. The % in vitro drug release from formulations F1, F2, F3, F4 and F5 at the end of 30 minute were found to be 88.61%, 91.64%, 93.80%, 96.21% and 97.82 respectively. Drug release kinetics parameters with n, R2 value are provided in table 4. According to the value of n the optimised formulation indicates super case II transport of drug release.

Table 3: Post-compression studies of pentoxifylline loaded chewable tablet

Formulation code	F1	F2	F3	F4	F5
Diameter(mm)	12±0.01	12±0.01	12±0.01	12±0.01	12±0.01
Thickness(mm)	3±0.01	3±0.01	3±0.01	3±0.01	3±0.01
% Wt. variation	400±2.5	400±2.0	400±3.2	400±2.8	400±2.6
Hardness (kg/cm2)	3.2±0.01	3.0±0.012	3.4±0.11	3.8±0.21	3.6±0.022
% Friability	0.88±0.11	0.35±0.21	0.55±0.31	0.49±0.33	0.39±0.021
Disintegration time (sec.)	80±0.22	72±0.31	48±0.34	30±0.21	24±0.43
Wetting time(sec.)	76±0.22	60±0.22	36±0.011	22±0.007	18±0.005
% *In vitro* drug release	88.61±0.004	91.64±0.01	93.80±0.031	96.21±0.009	97.82±0.009

Table 4:Release kinetics profile of Pentoxifylline Loaded Chewable Tablets

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer peppas (R^2)	Value of (n)
F1	0.6824	0.4370	0.9249	0.8143	1.100
F2	0.6507	0.4334	0.9028	0.8094	1.299
F3	0.6369	0.4297	0.9164	0.8067	1.159
F4	0.6133	0.4247	0.8826	0.8025	1.008
F5	0.6358	0.4271	0.9002	0.8028	1.073

DISCUSSION

The aim of preparation of chewable tablet is to provide drug formulations with the least adverse effects and maximal fast therapeutic effect. So it can improve patient compliance by producing drug effect more rapidly. To this end, chewable formulations comprise one of the major drug formulations, which have been studied through various parameters. Considering the comfort of patients in taking oral tablet formulations, the delivery system deserves receiving more attention in the treatment of peripheral vascular diseases.

Pre-compression evaluation parameters of pentoxifylline loaded granules

The granules were evaluated for various parameters as shown in Table 2. The value of angle of repose of all formulations ranges between 24.01-28.08˚ which shows very good powder flow properties as per the standard in compendia. The compressibility indices like Hausner's ratio and Carr's index value of granules produced acceptable values. This showed that granules from all the formulations having good flow property prepared by wet granulation method.

Post-compression evaluation parameters

The various parameters are to be taken under consideration for studies of evaluation of pentoxifylline loaded chewable tablets. Friability and hardness also affected by various concentration of diluent in the formulations. Mannitol containing formulations are more friable and less hard than lactose. On increasing the concentration of super disintegrating agent in various formulations, the disintegration time also increased [12].The *in-vitro* drug release of pentoxifylline loaded chewable tablets was found to be in the range of 88.61% to 97.62% from all

formulations. The thickness of pentoxifylline loaded chewable tablet was found to be 3±0.01mm. It depends upon size of die and punches, so it was uniform throughout the formulations (2, 3). The weight variation of chewable tablets was found to be in the range of 400 ± 2.0 to 400 ± 3.2. So, weight uniformity was maintained for all chewable tablets. The hardness of all formulations as found to be in the range of 3.0±0.21 to 3.8±0.65 kg/cm$^{2.}$ 1% starch solution provided sufficient hardness in pentoxifylline loaded chewable tablet which was required for this formulation. The variation may be due to variation in concentration of binder. On increasing the concentration of binder hardness also increases but it was found to be within the limits of chewable tablet. Tablets containing mannitol showed less hardness to the tablets containing lactose [15].The friability of all formulation code was found to be within the range of 0.28±0.01 to 0.88±0.03% i.e. all were within the acceptable limit. The disintegration time of chewable tablet formulations was depends upon the concentration of the superdisintegrant (SSG) in the formulation. On increasing the concentration of superdisintegrant more swelling was occurred which in turns enhance the disintegration of the tablet shown in fig. 1 [6, 16]. Wetting time actually depends upon the concentration of superdisintegrant which enhances wetting time by absorbing simulated fluid (i.e. phosphate buffer saline) through capillary action in the tablet [17].

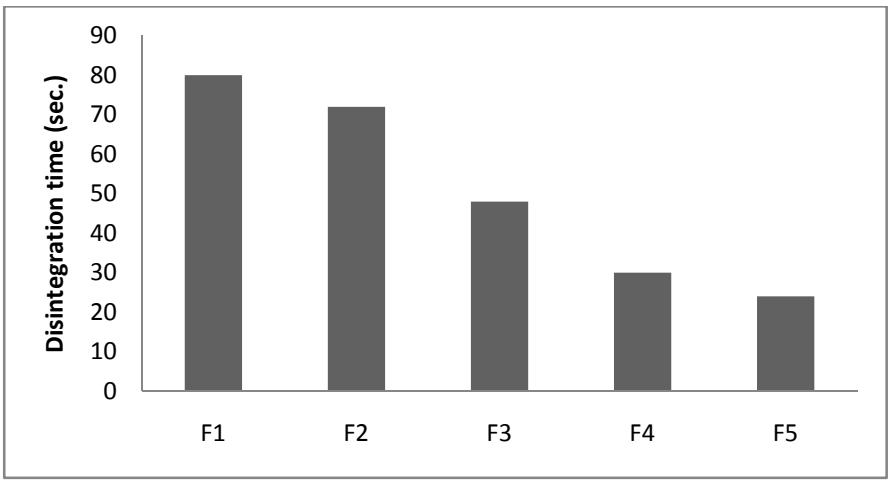

Figure 1: Disintegration time of pentoxifylline loaded chewable tablet (F1- F5)

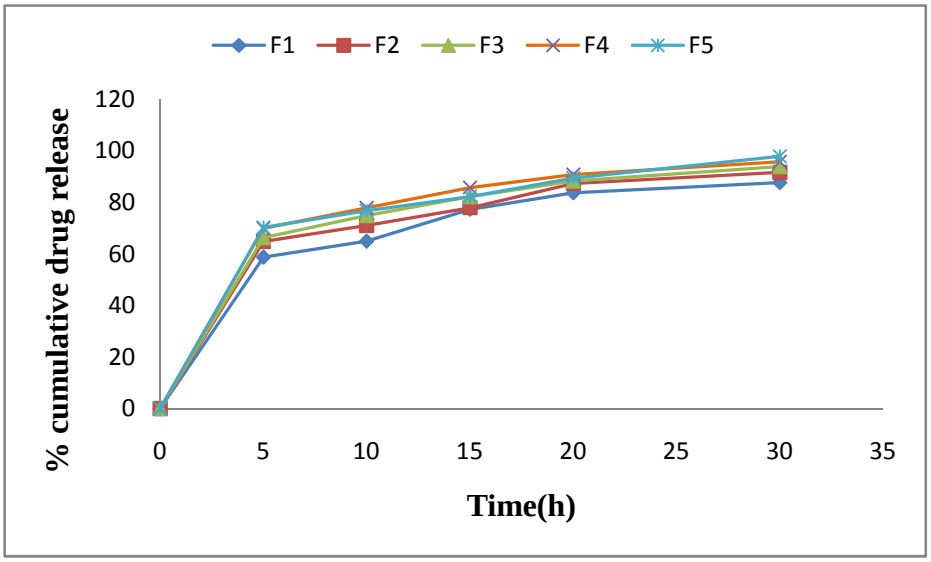

Figure 2: *In vitro* drug release profile of pentoxifylline loaded chewable Tablets

The cumulative drug release was found to be in the range of 88.61% to 97.62%. This may be due to swelling effect of SSG. In vitro drug release studies were carried out for 30 minutes and maximum release was found to be 96.42% of F5 formulation shown in fig. 2. On increasing the concentration of super disintegration in the various formulations, drug release also get enhanced. Swelling factor of SSG creates lacuna in the tablet and which increases the disintegration of the tablet [12, 18]. Dissolution data fit Higuchi's release kinetics given in table 4. The kinetics and mechanism of drug release was determined using zero-order, first order, Higuchi and Korsmeyer-Peppas model.

Regression (R^2) values were calculated for the linear curves obtained by regression analysis [19]. The in vitro release data was fitted into Higuchi's equation for determine the mechanism of drug release from the chewable tablet. When n value is 0.5 or less, the Fickian diffusion phenomenon dominates, and n value between 0.5 and 1 is non-Fickian diffusion (anomalous transport).

CONCLUSION

Pentoxifylline loaded chewable tablets were prepared using wet granulation technique and evaluated for various pre compression and post compression parameters. From the result, it was concluded that on varying the concentration of super disintegrant also get affected the disintegration time and in-vitro drug release. Lactose and mannitol produce significant effect on hardness and friability. Thus it can be concluded that pentoxifylline loaded chewable tablets using superdisintegrant can provide better therapeutic response for treatment of peripheral vascular diseases.

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