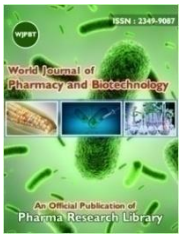

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Development and Evaluation of Multi-Layer Controlled Release Tablet of Pentoxifylline

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A b s t r a c t

In the present study an attempt was made to prepare Pentoxifylline Extended release tablet for the treatment of Peripheral artery disease. The drug excipient compatibility study was done and found to have no interactions. The precompression parameters (bulk density, tap density, Carrs index, and angle of repose) of the prepared tablets were within the ranges given by official standards, indicating that the physical mixture was found to be free-flowing. In vitro dissolution studies were done for Felodipine Extended release tablet prepared with different concentration of polymer HPMC K4M low viscosity grade and HEC high viscosity grade. Formulation F8 was found to be 94.75% drug release at the end of 12th hours which was within the USP limits. The kinetic of drug release for formulation F8 was calculated and plotted. The formulation F8 follows zero order release kinetics and the drug release mechanism was found to be non-fickian (anomalous) diffusion. The optimized formulation was compared with marketed product and showed similar release profile. The optimized tablets, F8 were selected for stability studies were carried out according to ICH guidelines at 40ºC /75 % RH for a specific time period indicated that the physical parameters and drug release characteristics were not altered significantly showing good stability on storage. The formulation containing 8% of polymer (6% of HPMC K4M and 2% of HEC) (F8 batch) followed the desired release profile and selected for further studies. The optimized formulation follows zero order release pattern (R2.9942 with rate of release 7%/hr) and the drug release mechanism was non-fickian (anomalous transfer). Therefore, swelling and diffusion mechanisms were found to be responsible for the prolonged release of pentoxifylline from formulated matrix tablets. The optimized formulation compared with marketed formulation, were found to have a similar In vitro release profile, which is confirmed by f1 and f2 values. In terms of physical properties and drug content, the formulation (F8) was found to be stable for 3 months under accelerated conditions

Keywords: Pentoxifylline, ICH guidelines, HPMC K4M, Carrs index

A r t i c l e I n f o

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C o n t e n t s

1. Introduction

Multilayered systems (bilayered, triple-layered, quadruple-layered, etc.) are becoming increasingly recognized as controlled-release drug delivery systems. These systems have been shown to be advantageous over typical tablet systems as depicted. Namdeo expressed that multi-layered tablets have demonstrated promise, possessing various benefits, namely the ability to prevent interactions between drugs and excipients; and by providing an array of release profiles in one delivery system of either the same or different drugs, treatment for conditions that require a regimen of more than one drug, immediate drug release using a disintegrating monolithic matrix in order to achieve an initial peak in plasma drug level, delayed drug release using an eroding monolithic matrix which may deliver another active drug to a different part of the gastrointestinal tract, providing controlled drug release instituting a swellable monolithic matrix and better control and regulation of release profiles by retarding initial burst release and achieving zero-order kinetics. Controlled-release multilayered tablets typically involve a drug core layer that is surrounded by barrier layers that may be made up of hydrophilic swellable polymers such as hydroxypropylmethylcellulose (HPMC) and poly(ethylene oxide) (PEO) or hydrophobic polymers such as ethylcellulose (EC).

The barrier layers minimize and therefore delay the interaction of the gastrointestinal environment with the active core, by decreasing the surface area available for drug release or by controlling the rate at which the solvent penetrates the layers. This allows the initial burst release to be minimized and therefore the drug release can be controlled at an ear constant level while the barrier layers undergo erosion or swelling. The swollen barrier layers undergo erosion as time goes on, thus increasing the surface area which ultimately allows more drug to be released. Following the same principle, it is possible to obtain a constant release profile as well as other types of dissolution patterns such as pulsatile or delayed delivery as well as extended drug delivery depending on the characteristics of the polymers employed. In either case the system should ideally erode completely.

2. Material and Methods

Pentoxifylline is procured by Cipla India Ltd.mumbai, Hydroxy propyl methyl cellulose K- 100 M is procured by Signet chemical corporation, Mumbai, Gelatin, Magnesium stearate, Magnesium stearate, Talc, Sodium benzoate, Lactose are procured by Loba chem., Cochin.

Preformulation Studies: Preformulation studies can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipient. Preformulation investigations are designed to identify those physiochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. It is the first step in the rational development of dosage forms.

Preparation of standard calibration curve of pentoxifylline:

25 mg of pentoxifylline was accurately weighed and dissolved in 25 ml of distilled water in 100ml volumetric flask and make up the volume using distilled water, to make (250µg/ml) standard stock solution. From the standard solution pipette out 1,2,3,4, and 5 ml into 50 ml volumetric flask and dilute them up to 50 ml with distilled water to produce concentration as 5,10,15,20,and25µg/ml respectively. The absorbance of standard solution was determined using UV/VIS spectrophotometer at274nm and distilled water as blank.

Drug-Excipient Interaction Studies:

The compatibility of drug and excipient is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipient under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

FT-IR Analysis:

Potassium Bromide Pellet (KBr) method was used in the study. Test samples were prepared by physical mixing of pentoxifylline and exicipients in ratios of 1:1. Initially 100mg of Potassium Bromide powder was mixed with 2mg of each sample, thoroughly triturated in mortar and pestle. A portion of mixture was compressed using IR pelletizing press. Then the KBr pellet was placed in sample holder of Bruker FT-IR spectrophotometer. The spectra were recorded in the wave number region of 2000-600cm-1. In each case the spectra was compared with the pure pentoxifylline spectrum to detect the interactions between drug and excipient.

Evaluation of Tablets

Weight Variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table and none deviate by more than twice the percentage shown.

Thickness

Twenty tablets were randomly selected form each batch and there thickness and diameter was measured by using digital vernier caliper.

Tablet Hardness

The crushing strength Kg/cm-2 of prepared tablets was determined for 10 tablets of each batch by using Monsanto tablet hardness tester. The average hardness and standard deviation was determined.

Friability Method

Twenty tablets were weighed and placed in the Electrolab friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were deducted and weighed again. The percentage friability was measured using the formula,

$\% F = \{1-(Wt/W)\} \times 100$

Where, % F = friability in percentage

W = Initial weight of tablet

Wt = weight of tablets after revolution

Uniformity of Content

Five randomly selected tablets were weighed and powdered. The powdered tablet equivalent to 20 mg drug in one tablet was taken and transferred in a 250ml flask containing 100ml of phosphate buffer pH6.8. The flask was shaken on a flask shaker for 24 hours and was kept for 12 hours for the sedimentation of undissolved materials. The solution is filtered through Whatman filter paper (0.45µm). 10ml of this filtrate was taken and appropriate dilution was made. The samples were analyzed at 274 nm using UV/Vis Spectrophotometer. The drug content was determined from the standard curve prepared at λmax 274nm.

In Vitro Dissolution Studies

In Vitro dissolution study was carried out using USP I apparatus (basket apparatus) in 900 ml of phosphate buffer pH6.8 for 12hours. The temperature of the dissolution medium was kept at 37± 0.5oC and the basket was set at 50 rpm. 1 ml of sample solution was withdrawn at specified interval of time. The absorbance of the withdrawn samples was measured at λmax 274 nm using UV/ Vis Spectrophotometer. The concentration was determined from the standard curve of pentoxifylline prepared in distilled water at λmax 274 nm.

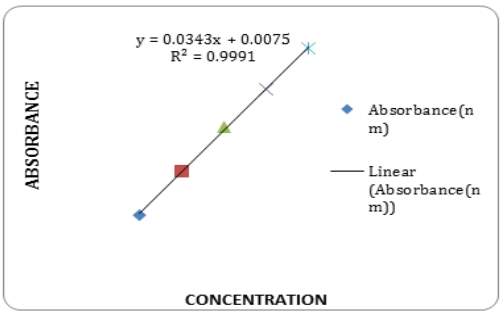

Figure 1: Calibration curve of pentoxifylline

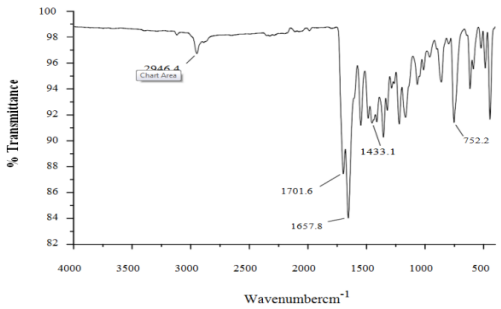

Figure 2: FT-IR Spectrum of Pentoxifylline

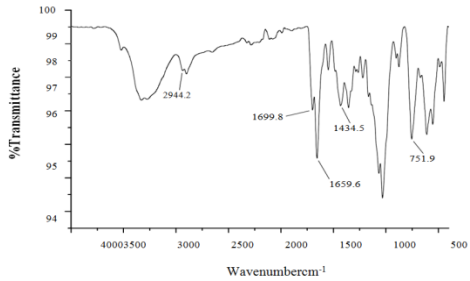

Figure 3: FT-IR Spectrum of Pentoxifylline with Excipients

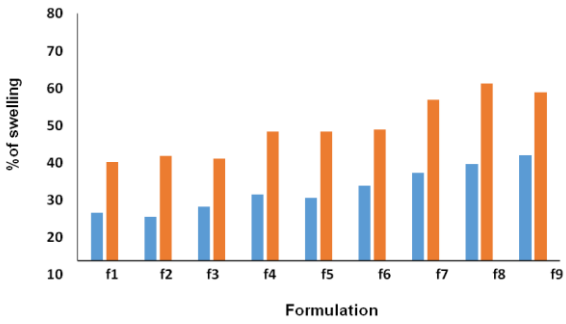

Figure 4: Swelling Index

3. Results and Discussion

Table 1: Evaluation of granules

Formulation	Bulk Density (g/ml)±SD	Tapped density (g/ml)±SD	Carr's index	Hausner's Ratio	Angle of repose(θ)
F1	0.420±0.13	0.478±0.12	12.32±0.49	1.10±0.01	24.39±0.18
F2	0.418±0.11	0.478±0.24	13.14±0.47	1.10±0.14	24.89±0.36
F3	0.425±0.14	0.487±0.11	13.56±0.13	1.26±0.02	25.60±0.28
F4	0.422±0.12	0.480±0.22	13.24±0.20	1.08±0.03	26.10±0.22
F5	0.426±0.11	0.488±0.18	13.46±0.10	1.14±0.04	27.40±0.16
F6	0.422±0.22	0.488±0.15	12.46±0.22	1.18±0.03	24.87±0.44
F7	0.427±0.22	0.482±0.26	12.80±0.30	1.16±0.05	26.90±0.59

F8	0.428±0.17	0.474±0.14	13.44±0.30	1.21±0.05	28.28±0.46
F9	0.424±0.23	0.478±0.17	12.98±0.56	1.18±0.06	24.98±0.41

Mean ± SD (n=3) The results show that all the formulation blends showed good low properties and can formuniform tablets.

Table 2: Calibration curve of Pentoxifyl line

S.No	Con.(µg/mL)	Absorbance(nm)
1.	5	0.172
2.	10	0.352
3.	15	0.535
4.	20	0.691
5.	25	0.86

Table 3: Evaluation of Core tablet

Formulations	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug content (%)
F1	602±0.32	5.3±0.05	7.2±0.06	0.12	99.31±0.17
F2	599±0.28	5.2±0.03	6.8±0.04	0.17	98.64±0.15
F3	600±0.32	5.2±0.02	7.0±0.07	0.17	98.86±0.13
F4	597±0.14	5.1±0.02	7.2±0.04	0.12	99.78±0.16
F5	605±0.26	5.4±0.05	6.8±0.07	0.21	98.80±0.06
F6	603±0.22	5.3±0.02	7.2±0.04	0.12	99.79±0.04
F7	600±0.16	5.2±0.03	7.0±0.03	0.10	98.83±0.13
F8	600±0.14	5.2±0.03	7.2±0.01	0.13	99.45±0.08
F9	598±0.21	5.1±0.02	7.0±0.05	0.12	99.87±0.12

Mean±SD(n=3) From the above post compression parameters the tablets were found to comply with the official standards.

Swelling Index:

Table 4: Swelling Index

Time(hr)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
1	15.5	14.30	17.5	21.50	20.35	24.27	28.50	31.21	34.2
2	20.34	18.34	20.23	27.39	25.23	27.23	33.21	39.40	38.34
3	24.14	22.38	23.80	29.59	29.20	33.27	38.56	43.80	42.31
4	29.98	27.40	26.45	33.26	32.46	36.23	45.59	49.50	46.04
5	28.30	30.23	28.46	35.62	38.42	39.21	48.20	53.30	49.60
6	31.98	33.80	32.91	41.87	41.10	42.45	52.16	57.43	54.57

Discussion

Pre-formulation:

The experimental work started with the raw material analysis of pentoxifylline as per USP, the physical properties such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose values were depicted.

Calibration curve:

The calibration curve of pentoxifylline was prepared in distilled water at determined wavelength at 274 nm. The r2 and slope were found to be 0.9995 and 0.03451.

FT-IR Studies:

The IR spectra of pure drug showed sharp peaks at 2945cm-1for–CH,1701cm-1for –CO, 1658cm-1 for amide −CO stretching, 1433cm-1 for –CH3, 752cm-1 for –(CH2)n−skeletal vibration. These peaks were found to be prominent in the spectra of physical mixtures containing the drug and excipients.

Evaluation of Physical Mixture:

Bulk density, Tapped density, Carr's index and Hausner's ratio, Angle of repose were evaluated for the prepared blend. The formulations F1 to F9, it shows good flow property. The angle of repose was found to be in the range 24.39◦ to 28. 28˚.Compressibility index was carried out, it foundbetween12.32 to 13.56, indicating the powder blend has the required flow property for compression. Hausner's ratio was calculated for the blend, it was found to be 1.10-1.26.

Evaluation of Core Tablet:

The hardness of tablets of each batch ranged between 6.8 to 7.2kg/cm2, this ensures good handling characteristics of all batches. Thickness of all the formulation was found to be in the range 5.10 mm to 5.40 mm. Friability of all the formulations were found to be in the range 0.12% to 0.21%. The percentage of drug content for F1 to F9 was found to be 98.64% to 99.87%, it complies with official specifications.

Determination of swelling index for Pentoxifylline:

Formulation F8 shows a higher swelling index due to the fact that the viscosity of the polymer has a significant effect on the swelling process. As can be seen from the above, since the polymer gradually absorbs water and swells due to its hydrophilicity, the swelling of the tablet goes through and swells with time, and the water absorption rate increases as the viscosity of the polymer increases. At the end, the polymer of the higher viscosity shows the maximum absorption.

Effect of HPMCK4M and HEC on drug release:

All the formulations were prepared by wet granulation technique. Different formulations were developed using different weight gain (4%, 6%, 8%) of polymer. Basically, HPMC and HEC is a hydrophilic polymer which controls the release rate of the drug for the extended period of time.

Effect of 4% weight gain by coating on drug release

For the formulation From F1-F3 containing 4% of HPMCK4M and HEC, the formulation F1 containing 2% HPMCK4M and 2% HEC, the release from the formulation was found to be 99.76% at the end of 8th hour which shows the release was not within the USP specification limit. Drug release was shown to be high due to low polymer concentration.

For the formulation, F2 containing 3% of HPMC K4M and 1% of HEC, the release from the formulations were found to be 99.56% at the end of 8th hour which shows the release was not within the USP specification limit. As the polymer concentration was low, the drug release shows high.

For theformulationF3containing 1% of HPMCK4M and 3% of HEC, the releasefrom the formulations were found to be 99.97% at the end of 8th hour which shows therelease was not within the USP specification limit. As the polymer concentration was low, the drug release shows high.

Effect of 6% weight gain by coating on drug release

Forthe formulation F4-F6, the polymer weight was increased to 6% of HPMC K4M and HEC, the formulation F4 containing 3% HPMC K4M and 3% HEC drug releasewere found to be 85.48%. The 4th hour not within the specified limits, but the releasewas improved compared to F3, the concentration of polymer concentration was high,which provides the slow release of drug, it was further reduced. Formulation F5 HPMC K4M was increased to 4% and HEC was reduced to 2%, therelease was found to be 84.85%, because high concentration of HPMC K4M. The 4thhour drug release was not within the USP limits. Formulations F6, the polymer was reduced to 2% of HPMC K4M and 4% of HEC therelease was found to be 88.66%. The 4th hour drug release was not within the USP limits.

Effect of 8% weight gain by coating on drug release: Hence, to meet the required release profile, polymer concentration was further increased 8% for the formulation F7 (4% of HPMC K4M and 4% of HEC), 96.56% of the drug was released at the end of 12 hours. The results showed that the drug release time was prolonged due to its polymer concentration.

Formulation F8 containing 6% of HPMC K4M and 2% of HEC, which shows 94.75%of the drug was released at the end of 12 hours. Furthermore, the polymer concentration was changed to the next trial. Finally, the release from the formulation F9 containing 2% of HPMC K4M and 6 % of HEC, which shows 97.69% at the end of 12th hour, which was within the USP limits.

When the amount of polymer was increased, the drug release was found to be decreased. The type and amount of polymer influenced the rate and release of the drug.WeretheformulationF1-F6 as shown controlled release but doesn't meet a USP specification. F7-F9 showed better controlled release than all of the above formulations, which were observed to meet USP specifications for extended-release tablets. Then the formulation F7-F9 was compared with marketed product, F8 shows similarity factor– 92. So, F8 was selected optimized formulation

Interpretation of Dissolution Profile:

The results of the dissolution studies indicated that the release was affected by the weight of the polymer. The polymer, HPMC K4M, HEC had a retarding effect with high concentration (amount). When the polymer weight is high, the drug release was found to be slow. Once there is a sufficient polymer weight is achieved in the core of the tablet or in the matrix system, dissolution give a uniform layer is formed to protect the drug release immediately into the dissolution medium.

Evaluation of coated tablet:

The optimized formulation F8 was observed. The thickness was found to be in the range 5.65mm. The hardness was found to be 7.2 kg/cm2. The percentage of drug content was 99.45%. Optimized formulation F8, the drug release was found to be 16.86%, 35.62%, 73.82% and 94.75% at the end of 1st, 4th, 8th and 12th hour which was within the USP limit. Formulation F9 shows the similar release profile to marketed product.

Release kinetic study for optimized matrix tablet:

Dissolution data of the optimized formulation was fitted to various kinetic models (zero order, first order, Higuchi and Korsmeyers Peppas) in order to describe the drug release profile. A plot of the cumulative percent drug release as a function of time shows that none of the formulations followed the first order or Higuchi Kinetics (Table:) the line of best fit obtained was zero order release kinetics (R2=0.9942) and Korsmeyers Peppas model, the drug release data further analyzed for curve fitting and the results(n=0.7062) confirmed that the formulation follows non–fickian (anomalous) diffusion kinetics.

Comparison between Optimized batch and Marketed product:

The optimized formulation F8 was compared with the commercially available product. In optimized formulation, the drug release was found to be 16.86%, 35.64%, 73.82% and94.75% at the end of 1st,4th,8th and the 12th hour was seened to be close to the marketed product, the drug release was found to be 17.44%, 36.46%, 74.37and 95.46%.

Similarity factor (f2) and dissimilarity factor (f1) was calculated between F8 and marketed product. Differential factor (f1) and Similarity factor (f2) was found to be 2and 92, which shows similar release profile to the marketed product.

Stability study:

Stability studies were conducted for the formulation F8. The stability study was performed at 40ºC /75 % RH/ 3 months. The tablets were analyzed for appearance, average weight, thickness, hardness, drug content and in vitro drug release. Overall results indicate that the formulation is stable under the above storage conditions.

4. Conclusion

The pre-compression parameters (bulk density, tap density, Carrs index, and angle of repose) of the prepared tablets were within the ranges given by official standards, indicating that the physical mixture was found to be free-flowing. In vitro dissolution studies were done for Felodipine Extended release tablet prepared with different concentration of polymer HPMC K4M low viscosity grade and HEC high viscosity grade. Formulation F8 was found to be 94.75% drug release at the end of 12th hours which was within the USP limits. The kinetic of drug release for formulation F8 was calculated and plotted. The formulation F8 follows zero order release kinetics and the drug release mechanism was found to be non-fickian (anomalous) diffusion. The optimized formulation was compared with marketed product and showed similar release profile. The optimized tablets, F8 were selected for stability studies were carried out according to ICH guidelines at 40ºC /75 % RH for a specific time period indicated that the physical parameters and drug release characteristics were not altered significantly showing good stability on storage.

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