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Development of Extended-Release Formulation of Ibuprofen Using Blends of Calcium Silicate and Polyvinyl Pyrrolidone as Tablet Matrix

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Abstract: A tablet matrix system was developed for ibuprofen and the influence of the polymer blend and concentration on the release rate of the drug was evaluated. Tablets containing different concentrations of calcium silicate and PVP (polyvinyl pyrrolidone) were prepared using direct compression and the weight uniformity, crushing strength, friability, drug content uniformity, dissolution profile, and *in vitro* release kinetics were examined. Formulated tablets were found to be within the official acceptable limits of physical and chemical parameters except for the thickness test that was below the conformation of extended-release tablets. The crushing strength of the tablets was in the range of 2.5 to 5.6 kg/f, the weight variations of the tablets of all the formulation was less than ± 5%. The friability of all the formulations was in the range of 0.6% to 1.83%. Tablet thickness and diameter was in range of 3.18 mm to 4.48 mm and 12.53 mm to 12.64 mm respectively. Absolute drug contents of all the formulations were found to be in range of 83.50% to 98%. The release kinetic of F3 containing 20 mg of calcium silicate, 40 mg of PVP as matrix formers showed the best linearity (r^2 = 0.6975) with % drug release of 96 showing that combination of the two polymers (20 mg calcium silicate and 40 mg PVP) for use as a matrix former is best for extended-release formulation of ibuprofen.

Key words: Calcium silicate, ibuprofen, ER (extended release), dissolution profile, release properties.

1. Introduction

The oral route is the most common route of drug administration because of its advantages in terms of convenient administration thus leading to increased compliance. To achieve and maintain the concentration of administered drugs within therapeutically effective range, it is often necessary to take drug dosage several times and these results in fluctuating levels in the plasma with conventional dosage forms [1]. To avoid this limitation, development of oral controlled release formulations is an attempt to release the drug intervals into the gastrointestinal tract and maintain an effective drug concentration in systemic circulation for a longer time [2]. Despite the many synonyms used to explain delivery strategies that maintain plasma steady-state, ER (extended release) is one of such nomenclatures that accurately describe drug delivery systems that help to achieve these intentions by continuously releasing the therapeutic actives over an extended period of time on single dosing, thereby giving a prolonged therapeutic effect.

In the matrix system, an active pharmaceutical ingredient is embedded throughout the polymer matrix of insoluble/hydrophilic substance [3]. Matrix tablets are the type of controlled drug delivery system which releases the drug in continuous manner. In matrix system the drug substance is homogenously mixed into the rate controlling materials. With improvement in technology, using tablet matrix as extended-release formulation, many drugs have been delivered in such a way that it improves safety, efficacy, but in some cases allows the new and more effective therapies.

There are some drugs which have long half-lives and hence are long lasting. They are required to be

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given once a day to maintain adequate blood levels and the desired therapeutic effects. On the other hand, there are some drugs which have moderate to short half-lives and therefore require multiple daily dosing in order to achieve the desired therapeutic levels. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses and patient noncompliance with the therapeutic regimen. Another drawback of multiple dosing is that when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy and if the doses are administered too frequently, minimum toxic concentrations may be recalled with toxic side effects resulting. If doses are missed, periods of sub-therapeutic blood levels or dose below the minimum effective concentration may result, with no patient benefit [4]. Extended drug delivery, the main objective to formulate an API (active pharmaceutical ingredient) in an extended drug delivery system is related to its pharmacokinetics parameters. An appropriate formulation can make the ADME (absorption distribution, metabolism and elimination) profile of a drug much more favorable.

Excipients modify the drug release characteristics and enhance the solubility and bioavailability of dosage form, impart weight, and increase patient compliance [5]. The introduction of new high-speed tablet machinery requires excipients with good compressibility, compatibility, flow properties and even short dwell times.

Calcium silicate, a porous carrier, is a white free-flowing powder. It can be derived from naturally occurring limestone and diatomaceous earth, a siliceous sedimentary rock. It is one of a group of compounds that can be produced by reacting calcium oxide and silica in various ratios [6]. It has a low bulk density and high physical water absorption. Calcium silicate is an excipient with a promising drug porous carrier owing to its excellent biocompatibility, good bioactivity and high drug-loading capacity. In recent years, studies have been carried out on the synthesis of calcium silicate and their applications in drug delivery, where very interesting results and important insights have been documented [7]. FLR (Florite) is easily dispersible in all aqueous fluids and has been used to adsorb oily and other drugs, as a compressive agent in pharmaceuticals, and to improve solubility [8].

Owing to a wide range of useful properties, porous carriers have been used in pharmaceuticals for many purposes including development of novel drug delivery systems such as floating drug delivery systems and sustained drug delivery systems; improvement of solubility of poorly soluble drugs; and enzyme immobilization. Examples of pharmaceutically exploited porous carriers include porous silicon dioxide (Sylysia), polypropylene foam powder (Accurel), magnesium aluminometa silicate (Neusilin), and porous ceramic [9]. A relatively newer group of carriers include porous carriers, which are low-density solids with open or closed pore structure and that provide large exposed surface area for drug loading. Their hydrophobicity varies from completely hydrophilic carriers, which immediately disperse or dissolve in water, to completely hydrophobic ones, which float on water for hours.

Standard OTC (over the counter) ibuprofen is taken as a 200 or 400 mg dose, which may be repeated every 4-6 h as needed up to a maximum of 1,200 mg/day. Ibuprofen is rapidly absorbed after single doses of regular-release preparations, with peak plasma drug concentration occurring within 3 h of dosing. Ibuprofen formulated in controlled released tablets is manufactured by fluid bed technique and wet granulation methods have been reported. However, the simplest method for designing controlled release dosage form is preparation of a drug embedded matrix tablet that comprises of direct compression of a blend consisting of the drug, retard materials and other additives. This system offers several advantages which include flexibility to provide a desirable drug release profile, cost effectiveness, broad regulatory acceptance as well as improve patient compliance

[10].

The aim of this project is to produce extended-release tablet matrix formulation of ibuprofen to help reduce the three times in a day dosing frequency to a single dose with equivalent bioavailability using calcium silicate and PVP (polyvinyl pyrrolidone) as a polymer blend and evaluate tablets produced.

2. Materials and Methods

2.1 Materials

Ibuprofen powder was obtained from Sigma Aldrich (St. Louis, MO, USA). Other ingredients used included calcium silicate Florite® (a gift from Tomita Pharmaceutical Co. Ltd. Japan), PVP (Kollidon® VA 64 Fine. Ludwigshafen Germany), Cellactose, hydroxypropylmethylcellulose (Hopkins and Williams Ltd, Stanheat Essex, England), Lactose Granulac® 140 (MEGGLE Group Wasserburg, Germany). All other materials used were of analytical grade.

2.2 Methods

2.2.1 Preparation of Granules

The granules were prepared using the direct compression method. Batches (7) of granules were prepared using different compositions of calcium silicate and PVP blend as tablet polymer with an equal quantity of ibuprofen in each batch as shown in Table 1. Batch F1 consisted of only PVP 4% polymer concentration, Batch F2 contained 2% calcium silicate and 6% PVP as polymer concentration, Batch F3 consisted of 4% and 8% polymer concentration, Batch F4 consisted of 6% and 10% of polymer concentration, Batch F5 consisted of 8% and 10% polymer concentration, Batch F6 contained only calcium silicate and 12% polymer concentration, Batch F7 consisted of 12% and 10% polymer concentration respectively. All the ingredients consisting of ibuprofen as API, calcium silicate, PVP, HPMC (hydroxypropylmethyl cellulose), cellactose and lactose in various quantities as stated in Table 1 were weighed accurately and mixed thoroughly in a porcelain mortar with pestle. Each batch was transferred to a well labeled zip lock bag ready for tableting.

2.2.2 Compression of Ibuprofen Extended-Release Tablets

The prepared granules, except for batch F6 were compressed using a single punch tableting press fitted with 12.5 mm fitted face punches (Cadmach Machinery Co. PVT. Ltd, Ahmedabad-45, India.) at a constant compression force of 15 kN.

2.2.3 Evaluation of Ibuprofen Extended-Release Tablets

2.2.3.1 Mechanical Properties

(1) Crushing Strength

The crushing strength of the tablets was determined using the Monsanto hardness tester (Rolex, Chandigarh). Five tablets from each batch were randomly selected and tested and the average calculated.

(2) Friability Test

The friability of 10 tablets was measured in a Roche friabilator (UNID 056830 Campbell Electronic, Mumbai, India). The tablets were de-dusted and weighed (W0) and then placed in the friabilator, which was then

Table 1 Composition of extended-release tablet of ibuprofen.

Ingredients (per tablet)	F1	F2	F3	F4	F5	F6	F7
Ibuprofen (mg)	300	300	300	300	300	300	300
Calcium silicate (mg)	-	10	20	30	40	60	60
PVP (mg)	20	30	40	50	50	-	50
HPMC (mg)	100	80	60	40	-	40	20
Cellactose (mg)	30	30	40	50	50	50	50
Lactose (mg)	50	50	40	30	60	50	20
Total (mg)	500	500	500	500	500	500	500

operated at a speed of 25 rpm for 4 min. Then the tablets were removed from the chamber de-dusted and reweighed (W1). The friability was then calculated using the equation below:

$$F = \frac{W0-W1}{W0} \times 100 \quad (1)$$

where, $W0$ is the initial weight of tablets before friabilation; $W1$ is the final weight of tablets after friabilation.

(3) Compact Density

Tablets density was calculated using mass, diameter, and thickness of five tablets selected randomly from each batch and by applying the equation below [11].

$$D = \frac{m}{\pi r2h} \quad (2)$$

(4) Tensile Strength

Tensile strength (T) was calculated using the crushing strength, diameter and thickness of five tablets from each batch and by applying Eq. (3) [12]:

$$T = 2F/\pi dt \quad (3)$$

where, F is the crushing strength, d the diameter and t thickness of tablets.

(5) Weight Uniformity Test

Ten tablets were randomly selected from each batch and individually weighed using an electronic balance (OHAUS, Galaxy). The mean, standard deviation and coefficient of variation were calculated.

(6) Thickness

This was done using five tablets randomly selected from each batch and the thickness measured using the micrometer screw gauge (KFW Scientific Industries, Ambala Cantt, India) and the average thickness was calculated.

(7) Diameter of Tablets

Five tablets from each batch were randomly selected and their individual diameters were determined using the micrometer screw gauge (KFW Scientific Industries, Ambala Cantt, India) and the average diameter was calculated.

2.2.3.2 Release Properties

(1) Tablet Dissolution Test

(a) Preparation of Dissolution Medium

HCl (0.1 N) was prepared by accurately weighing 4 g of HCl into a 1,000 mL volumetric flask. The HCl was dissolved in a little quantity of distilled water and the volume was made up to 1,000 mL with distilled water.

(b) Preparation of Ibuprofen Standard Calibration Curve

The standard concentration was prepared by dissolving 50 mg of ibuprofen powder in 50 mL of distilled water. This stock solution was serially diluted appropriately using 0.1 N HCl. The drug was assayed spectrophotometrically and a standard curve of absorbance vs. concentration was determined.

(c) *In Vitro* Dissolution Test

In vitro dissolution study was carried out using the United State Pharmacopoea (USP) basket method in the tablet dissolution test apparatus (DA-6D), at 50 rpm (revolution per minutes), in 900 mL of the dissolution medium containing 0.1 N HCl, maintained at 37 ± 0.50 °C 10 mL aliquot was withdrawn at 1.5 h, 3 h, 6 h, 9 h, 12 h, 18 h and 24 h intervals using a UV 2100 spectrophotometer (UV 2100 PC S/N 081126 BP 0807072, Shanghai, China). The assay was done at a wavelength of 265 nm, where ibuprofen exhibits peak absorbance. An equal volume of fresh medium was placed into the dissolution medium after each sampling, to maintain the constant volume throughout the test.

(2) *In Vitro* Kinetic Release Models of Ibuprofen Extended-Release Tablet

In order to investigate the drug release kinetics, the data obtained from *in vitro* dissolution studies were plotted into various kinetic models, which included zero order, first order and Higuchi model:

- Zero order kinetic model—cumulative % drugs released versus time;
- First order kinetic model—log cumulative % drug remaining versus time;
- Higuchi's model—cumulative % drug released versus square root of time.

The model with the highest correlation coefficient (R^2) was considered to be the best fit for the designated kinetic release.

(a) Absolute Drug Content of Ibuprofen Tablets

Ten pre-weighed tablets from each batch were crushed in a mortar. A powdered quantity equivalent to 300 mg was weighed out and dissolved in 100 mL of 0.1 N HCl in a volumetric flask. The solution was filtered using a Whatman filter paper No. 2, 0.1 mL of the filtrate was then measured and diluted up to 10 mL with 0.1 N HCl and analyzed spectrophotometrically at 265 nm using 0.1 N HCl as blank. The concentration of ibuprofen was then obtained by using standard calibration curve of ibuprofen.

(b) Mechanism of Drug Release from Ibuprofen Tablets Matrix

The mechanism of drug release was determined by plotting the percentage drug release fitted into Korsemeyer-Peppas model equation.

Korsemeyer-Peppas model—log cumulative % drug released versus log time.

3. Results and Discussions

3.1 FTIR (Fourier Transform Infrared) Spectra

The results of the FTIR of ibuprofen; PVP, cal silicate, ibuprofen; Cal silicate, ibu and PVP are respectively stated in Figs. 1-4. As shown in Figs. 1-4, the spectra of ibuprofen contain twenty-seven identifiable peaks, that of PVP alone showed fourteen identifiable peaks, while that of PVP + calcium silicate + ibuprofen showed twenty-two identifiable peaks and that of calcium silicate + ibuprofen showed twenty identifiable peaks.

3.2 Effect of the Various Formulations on the Physical Properties of ER Formulated Ibuprofen

The results of the weight variation, crushing strength, friability, thickness, and diameter as well as the content uniformity of the tablets produced are presented in Table 2.

Weight uniformity test is a pharmacopeia or official test which ensures consistency of dosage units during compression [13]. The maximum weight variation obtained in the weights of tablets from batch F1 to F7 was ± 0.03 and hence conformed to the British Pharmacopoeia specification which states that for tablets weighing greater than or equal to 250 mg, not more than two of the individual weights should deviate from the average weight by more than ± 5% and none should deviate by more than ± 10% [14].

From the study, the tablets crushing strength ranged from 5.6 kg/f to 3.1 kg/f for all formulation (F1-F7) which falls above the limit of not less than 3.0 kg/f for conventional tablets. Tablet hardness affects parameters like tablet disintegration, dissolution as well as the buoyancy properties of the tablet [15]. There was a significant difference in the tablet hardness as the proportion of the polymer increases. This is because hardness influences the compaction of substances in the tablets, the higher the hardness, the higher the compaction. A higher compaction causes much decrease in the porosity of the tablet matrix causing a retardation of solvent penetration into tablet core [16] with this it can be concluded that none of the batches had hardness strength to be harder than normal and so does not fit a criterium of an ER formulation.

The friability of all the formulations was in the range of 0.6% to 1.86%. The test of friability measures the ability of the tablet to withstand abrasion during packing, handling and shipping. The normal limit for tablet friability is less than or equal to 1% [14]. From the result of the study, the friability loss for all formulation was found to be within this stipulated limit. There was an observed increase in tablet friability as the proportion of the polymer increases [17]. The increased resistance of the matrices to fracture and abrasion as the polymer concentration increased could be attributed to the formation of more solid bonds [18].

Based on the results obtained the average tablets' thickness was 3.71 to 4.10 mm for F1-F7. Although tablet thickness is not in the pharmacopeia standards, it is important to be evaluated as it is one of the

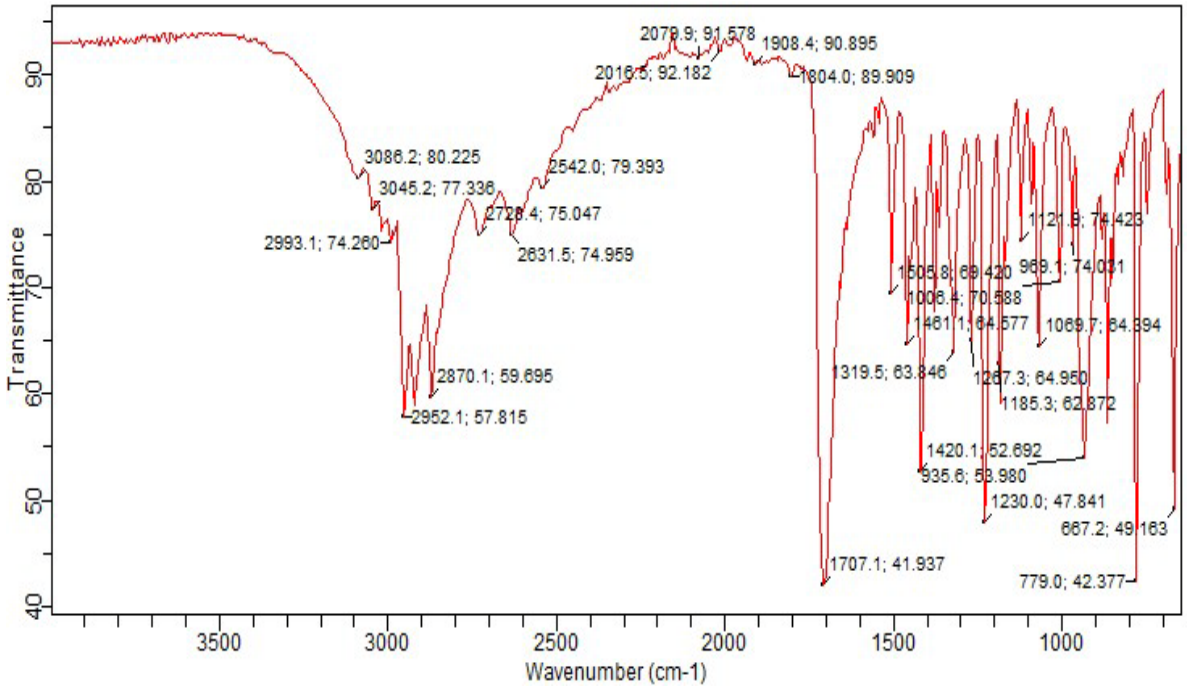

Fig. 1 FTIR spectra of ibuprofen.

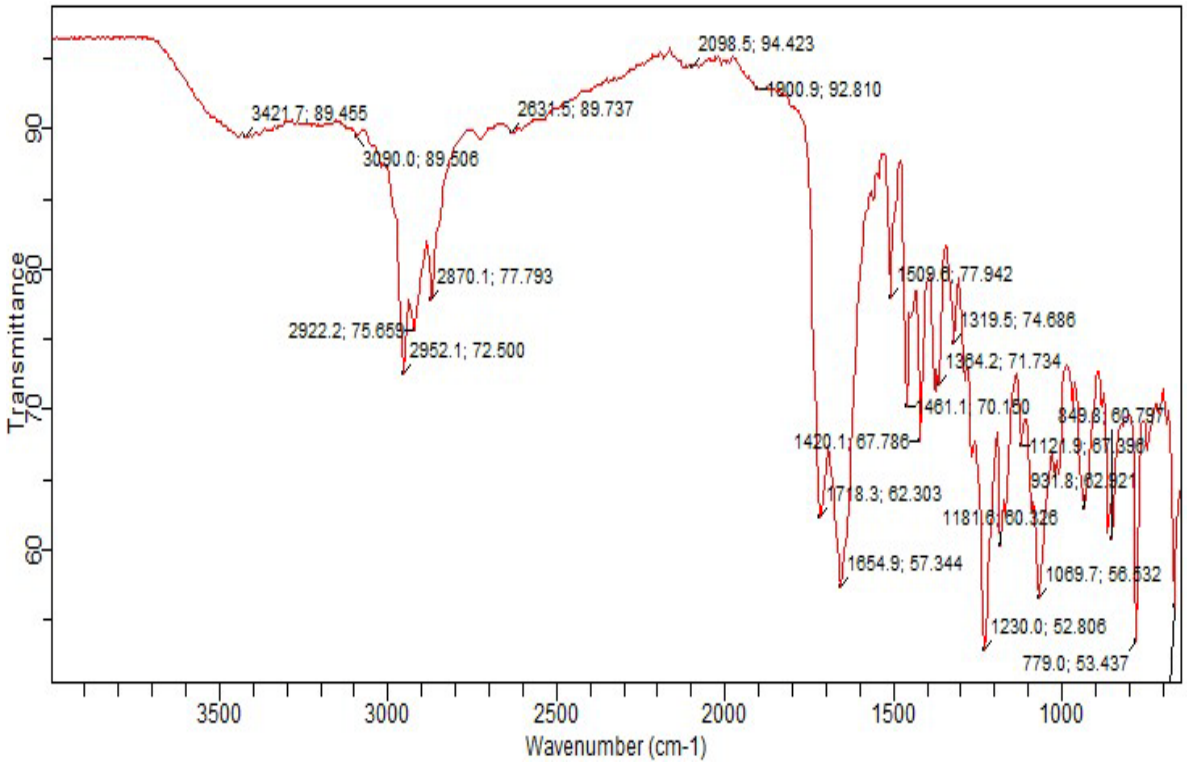

Fig. 2 FTIR curves of PVP + cal. silicate + ibuprofen.

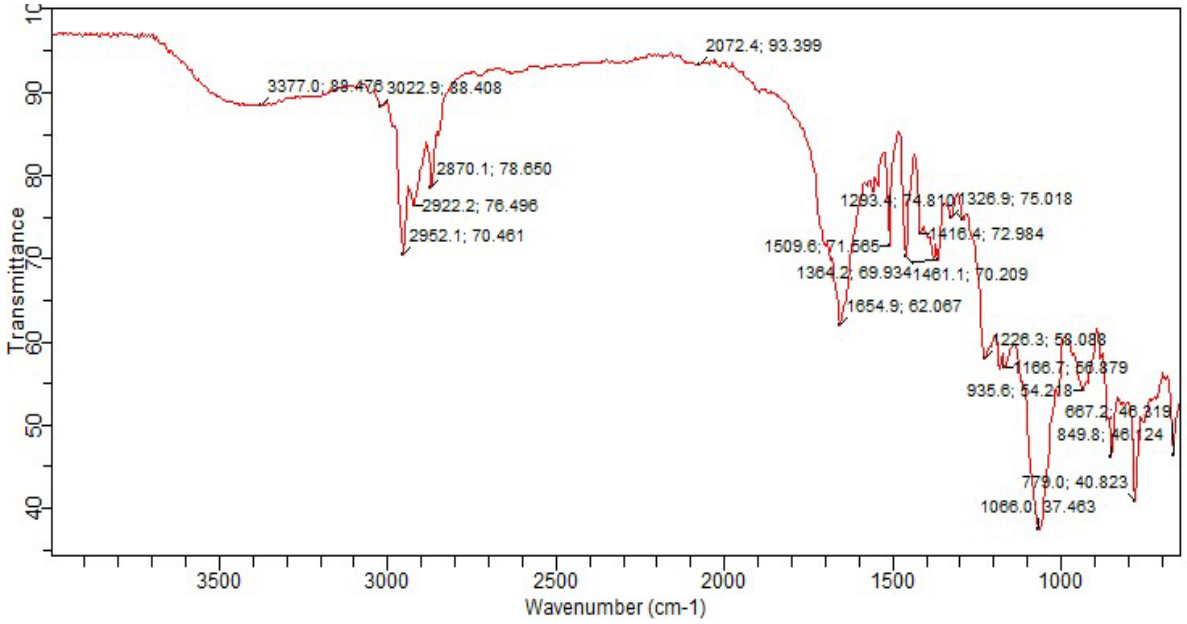

Fig. 3 FTIR spectra of cal. silicate and ibuprofen.

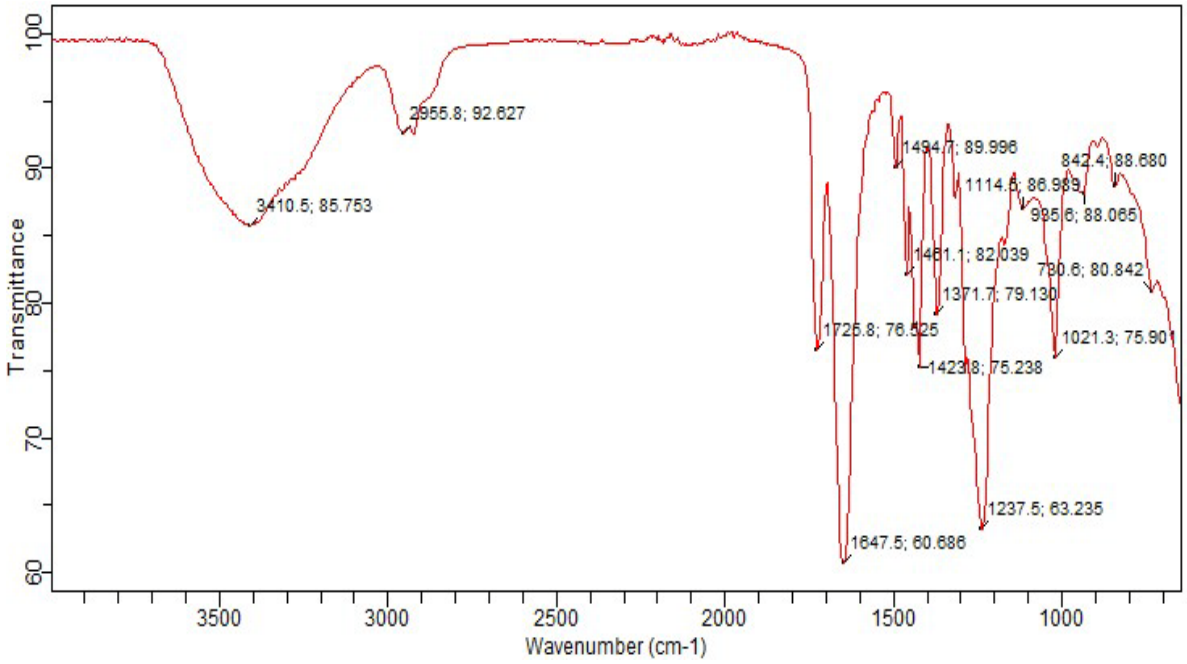

Fig. 4 FTIR spectra of PVP.

Table 2 Effects of the various formulations on the physical properties of ibuprofen extended-release tablets.

Batches	Weight variation Mean ±SD *n* = 10	Thickness (mm) Mean ± SD *n* = 5	Crushing strength (kgf) Mean ± SD *n* = 5	Friability (%)	Diameter (mm) Mean ± SD *n* = 5	Drug content (%)
F1	0.51 ± 0.02	3.89 ± 0.29	5.04 ± 0.36	0.78	12.58 ± 0.02	85.10 ± 0.51
F2	0.49 ± 0.01	3.68 ± 0.18	4.70 ± 0.59	0.90	12.59 ± 0.03	84.33 ± 0.79
F3	0.51 ± 0.03	3.92 ± 0.39	4.00 ± 0.35	0.67	12.55 ± 0.02	83.50 ± 0.11
F4	0.51 ± 0.03	3.71 ± 0.36	4.44 ± 0.37	0.62	12.58 ± 0.03	90.12 ± 0.80
F5	0.48 ± 0.02	3.73 ± 0.13	4.30 ± 0.44	1.18	12.58 ± 0.02	98.00 ± 0.40
F7	0.49 ± 0.03	4.10 ± 0.27	3.24 ± 0.48	1.83	12.58 ± 0.03	93.42 ± 0.19

methods to control the quality for packaging, meanwhile, the diameter is included in the standard which states that the deviation should not exceed ± 3% for tablets with diameter of 12.5 or more and as such from batch F1-F7 the average diameter lies between 12.55 to 12.59 mm and this shows conformation to the standard.

The slight variation in tablet thickness and diameter among the batches of tablets could be as a result of the varying density of the granulation [19].

The result of drug content for F1 to F7 was found to be in range of 83.50% to 98% respectively. These results are within the official limits [20], indicating proper mixing and processing of all the six batches.

3.3 Effect of Various Formulations on Tablet Properties

The effect of polymer ratio of tablet matrix former (calcium silicate: PVP) on compact density, tensile strength is shown in Table 3. There was a significance difference ($p > 0.05$) from the six compressed batches. There were no significant differences in the compact densities of F1, F2, F4, F5 and F7 and this was due to the fact that they were all tableted using the same compression force but that of F3 was seen to be different from the compact density of 0.003 although it used the same compression force as other batches. The tensile strength of F1 was the highest and other batches with a maximum deviation of ± 0.08.

3.4 In Vitro Dissolution Studies

The drug released was sustained for 24 h for all the compressed batches. The drug release profile as shown in Fig. 5 indicated that at the end of 24-h Batches F4, F5 and F7 had dissolved completely. However, there was an observation that the drug release rate was changing at each time interval during which an initial faster rate was seen and a subsequent decrease in the rate with time and an increase again. The percentage drug release at the end of 24 h was 105, 104, 96 for formulation F1, F2, and F3 while F4, F5, F7 had a percentage drug release of 97, 103 and 98 respectively.

3.5 Effect of the Various Formulations on Dissolution Constant and Release Kinetics of Ibuprofen Extended-Release Tablets

The result of the *in vitro* release kinetics and mechanism of extended-release formulation of ibuprofen tablet is shown in Table 4. The drug release data fit into different models like first order, zero order and Higuchi model to determine the kinetics of drug release and into Korsemeyer-Peppas model, in order to determine the mechanism of drug release. From the dissolution kinetics, all the batches did not follow any release kinetics except for F3 that tends to fit into Higuchi square root model.

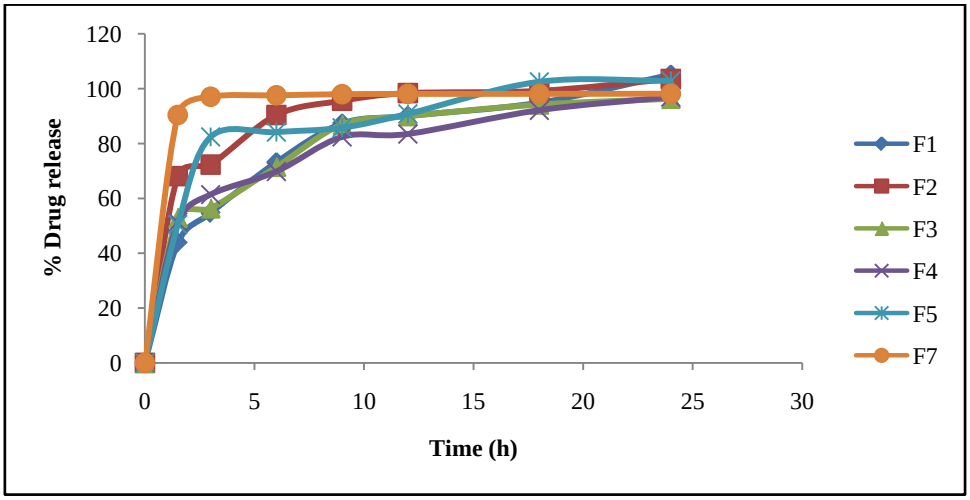

Fig. 5 The release profile of extended-release ibuprofen tablets with different polymer blend concentrations.

Table 3 Effect of matrix formers on tablet properties.

Batch	Calcium silicate: PVP (mg)	Compact density (g/cm^3)	Tensile strength (MN/m^2)
F1	0:20	0.001 ± 0.0001	0.07 ± 0.009
F2	10:30	0.001 ± 1.1	0.06 ± 0.005
F3	20:40	0.003 ± 0.004	0.05 ± 0.007
F4	30:50	0.001 ± 6.1E-05	0.06 ± 0.005
F5	40:50	0.001 ± 6.8	0.06 ± 0.002
F7	60:50	0.001 ± 0.0001	0.05 ± 0.008

Table 4 Effect of the various formulations on dissolution constant and release kinetics of ibuprofen extended-release tablets.

Batch	R^2			
	Zero-order	First order	Higuchi	Korsemeyer
F1	0.257	0.1359	0.3577	0.148
F2	0.230	0.1493	0.4027	0.135
F3	0.496	0.1154	0.6975	0.164
F4	0.449	0.1406	0.6208	0.156
F5	0.390	0.1454	0.5568	0.157
F7	0.221	0.1523	0.3577	0.171

4. Conclusion

Polymers are frequently used in drug delivery systems. By polymer combinations, formulators may be able to develop extended-release drug dosage forms for better performance than individual polymer preparations. Various polymer blends have been studied in order to achieve their desirable release kinetics [21]. In this piece of work, tablet matrixes were prepared using a blend of calcium silicate and PVP to enhance an ER of the drug ibuprofen and evaluating the mechanical and release properties of this tablet was observed to follow the standard in pharmacopeia. The drug release rate was changing at each time interval during which an initial faster rate was seen and a subsequent decrease in the rate with time and an increase again. The drug release was found to be best fitted by Higuchi square root model (r^2 = 0.6975) of F3 ibuprofen extended-release tablet which implies that release of drug from matrix as a square root of time dependent process and diffusion controlled. The *in vitro* studies suggest that this system has the potential to maintain a constant plasma concentration of ibuprofen over 24 h, which could reduce the frequency of administration and the occurrence of adverse effects associated with repeated administration of conventional ibuprofen tablets as shown in F3.

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Conflict of Interest

Authors declare no conflict of interest.

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