Design and formulation of piroxicam tablets

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ABSTRACT

Piroxicam is a potent nonsteroidal anti-inflammatory drug (NSAID) with a long half-life that permits once daily dose. It exerts a better toleration than other NSAID's with a relatively low incidence of adverse effects. In this study many trials were made to formulate piroxicam as plain tablets with properties comparable to those of capsules and in agreement with pharmacopoeial standards. Different formulas were prepared by the application of direct compression method and wet granulation method with the addition of different excipients. The wet granulation method used in the preparation of piroxicam tablets was modified to improve the properties of the produced tablets. The characteristics of the prepared formulas were tested and the results showed that formula D prepared by wet granulation method, containing PVP as binder and lactose as diluent is the most appropriate formula with a rapid disintegration time and complete dissolution as that of piroxicam capsules.

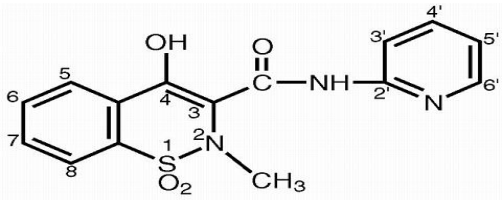
Accordingly, formula D was chosen to be a promising formula of piroxicam plain tablet that could be manufactured as a mass product.

الخلاصة

يعتبر البايروكسيكام من مجموعه الأدوية غير الستروديه المضادة للالتهابات وهو دواء فعال وذو مفعول طويل الأمد ويعطي بجرعة واحدة يوميا و يظهر تأثيره العلاجي مع قليل من التأثيرات الجانبية. في هذه الدراسة تم أجراء عده محاولات لتصييغ هذا الدواء بشكل أقراص لها صفات مماثلة لتلك الخاصة بالكبسول و مطابقة لدساتير الأدوية، وقد حضرت عدد من الصيغ باستخدام طريقة الضغط المباشر وطريقة التحبيب الرطب مع مضافات متعددة ومختلفة، كما تم أجراء بعض التعديلات على طريقة التحبيب الرطب التي كانت هي الطريقة المختارة في تصنيع هذا المستحضر. وبدراسة صفات الحبوب التي أنتجت للصيغ المختلفة أشارت النتائج إلى أن الصيغة (D) (المحضرة بطريقة التحبيب الرطب) والتي احتوت على ماده البولي ڤنيل بايروليدين (PVP) كماده رابطه وسكر اللاكتوز (Lactose) كمادة مخففة لها وقت تفتت سريع وإذابة كاملة مماثلة لتلك الخاصة بالكبسول وهي الصيغة المثالية لهذا المستحضر. لذلك اختيرت هذه الصيغة لتحضير هذا الدواء بشكل أقراص. وعليه يمكن الاستنتاج بان التركيبة (D) هي الصيغة الواعدة ومن الممكن أن تستخدم في إنتاج هذا الدواء وبشكل أقراص مماثلة لمستحضر الكبسول المنتج من قبل نفس الشركة.

Piroxicam is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAID's) and it has the advantage that once-daily dosage is sufficient to provide efficacy equal to or better than other NSAID's.[١] The toleration profile of piroxicam is typical of an inhibitor of prostaglandins, with a relatively low reported incidence of adverse events necessitating discontinuation of the therapy.[٢] In addition to that piroxicam exhibits better toleration than indomethacin, and enteric coated acetylsalicylic acid and is as well tolerated as diclofenac, naproxen, and ibuprofen.[٣-٥]

Piroxicam ($C_{١٥}H_{١٣}N_٣O_٤S$) has a molecular weight of about ٣٣١.٣٥ with the following structural formula.[٦]



٤-hydroxy-٢-methyl-N-pyridinyl-٢H-١,٢-benzothiazine-٣-carboxamide١,١-dioxide

Piroxicam is known to exist in different polymorphic forms and as a monohydrate, with specific solubility and stability parameters. Differences in dissolution rates among crystal forms of piroxicam were attributed to differences in their wettability, where highest wettability was obtained for monohydrate.[٧,٨]. The ester of piroxicam with pivalic acid exists in two polymorphic forms as well. [٩,١٠]

Although the oxicams are acidic compounds, they are somewhat less acidic than carboxylic acid NSAID's. Oxicams are primarily ionized at physiologic pH and acidity is required for COX inhibitory activity. [١١]

Piroxicam present in the market as capsule oral dosage form only and since tablet is the most commonly used oral dosage forms with manifold advantages,[١٢,١٣] so our purposes were to design and formulate piroxicam as a plain tablet that meets the pharmacopoeial requirements and to monitor tablet production quality.

Materials

Piroxicam powder was purchased from (Indiamart Intermesh Ltd., India), Maize Starch B.P. (Evans medical Ltd. Liverpool, England), Polyvinyl pyrolidone (PVP) (BDH chemicals Ltd., pool, England), Microcrocrystalline Cellulose (Avicel®) pH ٣٠٢ (Techno. Pharm. Chemical Delhi, India), Magnesium stearate (Barlocher, GmbH, Germany), Lactose monohydrate (Riedel-Dehaena Seelze-Hannover), Talc (Kline Asia, China), Stearic acid (Meade-king, Robinson Ltd.,Liverpool), Ethanol (Gapuma Ltd, UK), Mannitol (SPI Pharma Group, USA), Aerosil (Stochem specialty chemicals, Canada), Piroxicam capsule ٢٠mg (SDI, Iraq). The instrument used were Oven from (Gallenkamp, USA), Compressing machine (Airpac Exports, India), Friability tester (Erweka, GmbH, Germany), Tablet hardness tester (Erweka, TBH ٢٨, GmbH, Germany), Dissolution rate tester (Pharma test, PT-DT٧, Hainburg, Germany), Disintegration tester (Pharma test PTZ S, Hainburg, Germany), U.V. spectrophotometer (Cecil CE ٣٠٢١, Nile establishment for medical & laboratory supplies, Canada), High Performance Liquid Chromatography (HPLC) (Konik room, Espania).

Methods

Formulation of Piroxicam Tablet:

Different formulas of piroxicam tablets (٢٠ mg), have been designed to find the most appropriate method and formula.

To achieve our goal the first formula (A) was prepared by using direct compression method in which all the contents of the formula were mixed together and compressed using direct compression machine (Table-١).

The other three formulas (B, C and D) were prepared by wet granulation method (Table-١) which involves mixing the content, adding a solution to produce a damp mass and then transferring the masses to a tray dryer. The dried masses were sized by milling, screening then mixed with the other additives and finally compressed.

The general method of wet granulation was modified to improve piroxicam homogeneity with other additives by using ethanol instead of water in wetting the mass as well as changing the sequence of addition of the additives to the formula. This modified process was accepted and followed in preparing formula D of this product.

Evaluation of Piroxicam Tablets

Disintegration Test

The disintegration test was done according to British Pharmacopoeia test for plain tablets and by using Pharma test PTZ S disintegration tester(٦). Six tablets per batch chosen randomly were analyzed in distilled water which was the disintegration medium at ٣٧°C ± ٠.٥ºC. Tablets must disintegrate within the time set for each product in the individual monograph(١٤), known that piroxicam monograph is not less than ١٥ minute.[٦,١٥]

Dissolution

The dissolution test for piroxicam tablets was conducted using apparatus I (basket apparatus) and the dissolution media were distilled water and ٠.١N HCl solution. [٦,١٥] The dissolution medium was ٩٠٠ ml maintained at ٣٧ºC. The apparatus was adjusted to make the basket rotate١٠٠ times per minute, for ٤٥ min.[٦,١٥]. A ١٠-ml samples were withdrawn from each chamber and filtered. The concentration of piroxicam in each sample was evaluated by measuring the absorbance in each sample at ٢٤٢ nm.(λ max of piroxicam)[٦,١٥] using Cecil ١٠٢١ spectrophotometer. The monograph is not less than ٧٥%.[٦,١٥]

Weight Variation Test

This test was run by weighting ٢٠ tablets chosen randomly individually, calculating the average weight, and comparing the individual tablet weight to the average.[٦] The thickness of a tablet was measured using hand gauge appartus(micrometer).

Content Uniformity

Piroxicam tablets uniformity test was conducted by using high performance liquid chromatography (HPLC). The test solution was prepared by mixing the contents of ٢٠ crushed tablets containing ٢٠ mg of piroxicam with ١٥٠ ml of ٠.٠١N methanolic hydrochloric acid, the mixture was deaerated for ٣٠ minutes. The mixture was cooled and diluted to ٢٠٠ ml with the same solvent, filtered through glass-fibre paper and the filterate was used as a test solution. The standard solution contains ٠.٠٠٥% w/v of piroxicam BPCRS in ٠.٠١N methanolic hydrochloric acid. The mobile solution is ٦٠:٤٠ methanol:phosphate citrate buffer (pH ٦.٤). The chromatographic procedure was carried out using a stainless steel column (٣٠ cm×٣.٩ mm) packed with octadecylsilyl silica gel for chromatography (١٠μm)(μBondapak $C_{١٨}$). The flow rate was ٢ ml per minute and a detection wavelength of ٢٤٢ nm (λ max of piroxicam)[٦].

Hardness and Friability

The hardness and friability of all the prepared formulas have been tested according to British Pharmacopoeia[٦]

Table ١: Different formulations of piroxicam with their tableting methods

Constituents per tablet	Formula A	Formula B	Formula C	Formula D
Piroxicam	٢٠mg	٢٠mg	٢٠mg	٢٠mg
MCC (binder)	١-١٥%	ـــ	ـــ	ـــ
MCC (disintegrant)	ـــ	ـــ	٢-١٠%	٢-١٠%
Maize starch (binder)	ـــ	٥-٢٥%	٥-٢٥%	ـــ
Maize starch (disintegrant)	٣-١٥%	٣-١٥%	٣-١٥%	٣-١٥%
Lactose (diluent)	ـــ	٦٥-٨٥%	٦٥-٨٥%	٦٥-٨٥%
Stearic acid (lubricant)	ـــ	١-٣%	ـــ	ـــ
Mag.stearate (lubricant)	٠.٢٥-١%	ـــ	٠.٢٥-١%	٠.٢٥-١%
Mannitol (diluent)	١٠-٩٠%	ـــ	ـــ	ـــ
PVP (binder)	ـــ	ـــ	ـــ	٢-١٠%
Aerosil (glidant)	ـــ	٠.١-٠.٥%	ـــ	ـــ
Talc (glidant)	١-١٠%	ـــ	ـــ	ـــ
	Dry Compression	Wet Granulation	Wet Granulation	Wet Granulation

Table ٢: Properties of the prepared formulas of piroxicam tablets

Formula	Dissolution in D.W. (%)	Dissolution in HCl (%)	Disintegration time in D.W. (Sec)	Friability %	Hardness Sc*
A	٥٤.٨	٦٨	٤٠	١.٥٦	٧
B	٧٤	٨٢	٥٨	٠.٣٢	٧
C	٤٤.٨	٢٢	٣٨	٠.٣٤	٦
D	٨٩	١٠٢-١١١	١٠٧	٠.١٥	٩
Piroxicam capsule standard		Not less than ٧٥%	Not more than ١٥ min	Not more than ١.٥%	

*strong cob

Results and Discussion

Several types of formulas were designed to be prepared by different tableting methods depending on the optimum performance of the excipients which depends on many factors, including the physio-chemical properties of the drug, type of filler and the process used to make the tablet. The prepared formulas with their excipients and methods are seen in Table-١.

Direct compression method (DC) is still considered as a more economical method than the other methods with respect to time, space, materials and fewer steps in which the effect of heat and moisture is avoided.[١٦] So it is a process of choice in case of those drugs that are sensitive to heat and moisture. Formula A was designed and prepared by this method in which microcrystalline cellulose (MCC)(Avicel) was incorporated as a binder to ensure a mechanical strength of the mixture. Avicel is commonly used as a filler-binders in DC method, giving the tablet its self-disintegrating properties and it require little amount of lubricant[(١٣)]. The problem faced in this formula was its low flowability, which has been solved by the addition of ١-١٠% talc that acts as a glidant. It was stated that the addition of talc will improve the poor flow of powder from the hopper through the feed frame. [١٧]. Talc is widely used as a flow regulator of powders as well as using it to improve the lubrication function during compression.[١٧,١٨]

Although the addition of talc improves the powder's flow but unfortunately this formula (A) failed to meet the USP requirements as shown in Table-٢ except the hardness and friability of this formula which were within the accepted limits. The problem was with its disintegration which was very fast and such a fast disintegration is unacceptable because this may result in break up of the tablet on the mouth or oesophagus which might cause mucous membrane ulceration and may disturb the absorption of the active compound. The dissolution of this formula was less than the accepted limits which could be due to an increased time of blending of magnesium stearate which leads to a decrease in the dissolution rate and increase the tablet friability.[١٩]

The other three formulas (B, C, D) were manufactured by the wet granulation method. The results of the physical properties of the produced tablets of formula B (Table-٢) seemed to be accepted because it was near the standard limits. However, this formula was refused because it was not stable for a long period of time. The properties of formula B which were near the accepted limit could be due to the presence of aerosil in the core of the tablet (internally). It was stated that tablets friability, disintegration and dissolution rates will be increased by the incorporation of aerosil internally[(٢٠)].

By evaluating the properties of formula C, the results (Table-٢) showed that this formula failed to meet the pharmacopoeial specifications. It had very poor dissolution properties which will affect its bioavailability although formula C contains starch as a binder[٢١]. The poor dissolution of formula C could be due to magnesium stearate which was used in a high concentration in this formula. It was mentioned that the usage of magnesium stearate as a lubricant in a high concentration may results in a reduction in the disintegration time and retard drug dissolution.[١٢]

Formula D was prepared by wet granulation method with some modification in the process. It was designed to contain PVP in its core as a binder (Table-١) and the wet mass was prepared using alcohol instead of water as well as some changes in the steps of addition of the constituents. The results of Formula D shown in Table- ٢ indicated that the method used in the preparation of this formula was succeeded in getting a product with a required properties. PVP is one of the most commonly used pharmaceutical binders. It is not soluble in water, so a solvent must be used to carry the PVP particles in a liquid solution[٢٢]. PVP was added to formula D in a liquid state which not only enhances the bonding properties between particles or granules, but also improves the binding between powder particles during agglomeration.[١٣]

The good properties of formula D could be attributed also to starch which was incorporated into this formula as a intragranular and extragranular disintegrant.[٢٣]

According to all these results formula D was chosen to be the goal formula of piroxicam tablet to be studied thoroughly.

Piroxicam tablets (formula D) appeared as shallow biconvex uncoated tablets which have a pale yellow colour. The thickness of tablet of formula D was about ٣.٢ mm which comply with the required specification (٣mm ± ٠.٤mm), and the tablets diameter was ٧.١ mm which is also within the accepted limit (٧mm ± ٠.١mm). The weight variation of piroxicam tablet was studied and it was found to comply with the pharmacopoeial requirements (± ٧.٥%). Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance and high bioavailability.[٢٤] It was stated that the tablet hardness is perhaps the more important criteria since it can affect tablet disintegration and drug dissolution.[٢٥] The hardness of formula D was ٩ Sc which is within the accepted limits (٥-٩ Sc) (Table-٢). The tablets friability should not be more than ١.٥% and this was achieved in formula (D).

According to this accepted limits of hardness and friability, one could expect an accepted disintegration and dissolution time which might lead to an accepted bioavailability.

From Table ٢ it is clear that formula D has a disintegration time consistent with the pharmacopoeial specifications of piroxicam[٦,١٥]. This could be related to the addition of MCC which leads to the production of a tablet with a rapid disintegration. It was stated that MCC addition leads to rapidly disintegrating tablets with a high tensile strength[١٣]. The acceptable disintegration could refer to the addition of starch which was incorporated in this formula to act as a double disintegrant and thus can improve tablet disintegration.[١٤,٢٣].

The dissolution test is an extremely valuable tool in ensuring the quality of a drug product. From Table ٢ it is clear that formula D have a relatively good dissolution pattern in D.W. which could be due to the presence of PVP. The dissolution pattern of formula D in ٠.١N in comparison with the other formulas indicated that these tablets are completely dissolved within the specified time of the test and it comply with the USP requirement which could be related to the presence of PVP. It was mentioned that a significant increase in the dissolution of piroxicam could be due to its dispersion in PVP[٢٦]. Also the addition of an extragranular MCC tended to increase both dissolution and compactibility of the granules. It has been proved that the appropriate distribution of MCC between and within granules may optimize both dissolution and compactibility without changing overall tablet composition.[٢٧]

The high dissolution could be also due to maize starch used in all formulas because it produces tablets with high properties.[٢٨]
Although all formulas contained maize starch, only formula D succeeded in the dissolution test which could be attributed to the presence of PVP with maize starch.

It was stated that the addition of maize starch can lead to a highly efficient processing, resulting in strong benefits for final tablet properties; which include high mechanical resistance as well as excellent disintegration and dissolution properties [٢٨] and when the concentration of starch was increased a progressive increase in the dissolution rate was noticed[(٢٥)]. The improved dissolution noticed in tablets of formula D could be also attributed to alcohol (ethanol) which was used as a solvent for preparing the granules.

There was a correlation between the decrease in dissolution with an increase in water content (the mechanism of this change was not clear). [٢٩]

The usage of alcohol as a solvent instead of D.W. could also explain the good properties of this formula as compared with formula B and C which are manufactured by the same method (wet granulation). The poor dissolution of formula C compared to that of D could be due to the concentration of magnesium stearate.
The dissolution of plain tablets of formula D was compared with that of capsule produced at the same factory (SDI) and the result was as follows:

Piroxicam capsule	٨٩.٨٨% - ٩٩.٤%
Piroxicam tablet (Formula D)	١٠٢-١١١%

The result of the content uniformity assay of piroxicam tablets using HPLC showed that there was a little difference between this product and the standard piroxicam powder. In comparing the uniformity of piroxicam tablet (formula D) to that of piroxicam capsule prepared at the same factory, the tablet content was found to be (٩٩%) compared to (٩٥.٦%) of capsule, both compared to the specific limits (٩٥%-١٠٥%).
Both products (tablet & capsule) were labelled to contain ٢٠mg of piroxicam. The concentration of piroxicam found in the prepared tablets was ١٩.٨mg compared to ١٩.١mg found in capsule. From all these results it seems that formula D is a promising formula and we have succeeded to get a plain tablet formula for piroxicam with higher specifications.

Conclusion

Piroxicam is a potent nonsteroidal anti-inflammatory drug that can be formulated as a plain tablet dosage form. The wet granulation method is the method of choice to get a tablet with standard specifications. The end result was the formulation of a product that is comparable to the reference drug (piroxisam capsule ٢٠ mg). Formula D can be approved as a formula of choice for piroxicam tablets.

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