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(54) Title: A process for the preparation of a orally administered unit dose tablet

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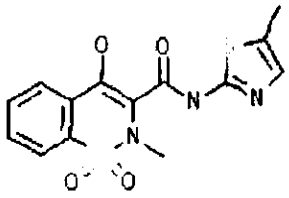
"A Process for the Preparation of an Orally Administered Unit Dose Tablet"

Field of the Invention

The present invention is directed to a process for preparing an orally administered palatable unit dose tablet comprising meloxicam and to an orally administered palatable unit dose tablet comprising meloxicam.

Background to the Invention

Meloxicam is a member of the enolic acid group of NSAIDs. Its chemical name is 4-hydroxy-2-methyl-N-(-5-methyl-1,3-thiazol-2-yl)-2H-1,2 benzothiazine-3-carboxamide 1,1-dioxide. It has a chemical formula of $C_{14}H_{13}N_3O_4S_2$ and a structure as follows:



It has a molecular weight of 351.403 g/mol, a melting point of 254 °C. It is a solid and is insoluble in water and soluble in dimethyl formamide.

Meloxicam is a non-steroidal anti-inflammatory drug NSAID that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. Prostaglandins are substances that contribute to inflammation of joints. Meloxicam inhibits prostaglandin synthetase (Cyclooxygenase inhibitors 1 and 2) and leads to a decrease of the synthesis of prostaglandins, therefore, inflammation is reduced. Anti-inflammatory effects of meloxicam are believed to be due to inhibition of prostaglandin synthetase (Cyclooxygenase inhibitors 1 and 2), leading to the inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of their synthesis may be associated with the analgesic and antipyretic effects of meloxicam

Meloxicam has the following general activities:

- Analgesics
- Antineoplastic Agents
- Antiemetics
- Nonsteroidal Antiinflammatory Agents (NSAIDs)
- Cyclooxygenase Inhibitors
- Growth Inhibitors

As such, it may be used in the treatment of arthritis and osteoarthritis.

Meloxicam is presently sold as an oral suspension and in a tablet form for oral administration. In the pharmaceutical field, much effort and expense is invested in developing new pharmaceutical formulations. Much of the expense stems from the necessity of performing studies to ensure safety, efficacy, and bioequivalence prior to marketing the drug. Any process which can reduce these costs will provide a significant commercial advantage to a pharmaceutical company.

The general process for the manufacture of commercially available Meloxicam tablets is by wet or dry granulation. Wet granulation specifically improves the flow properties of the poor flow and high percentage of active material content and reduces the potential for the segregation of the ingredients and is widely used in the pharmaceutical manufacturing of tablets. However, wet granulation involves extra processing steps and additional equipment costs. Specifically, wet granulation involves further manufacturing steps including wet mixing, making a binder solution, drying and milling. Furthermore, the extra handling of the ingredients in these additional processing steps leads to more process loses.

Furthermore, another problem associated with the large-scale manufacture of meloxicam tablets is to produce a tablet with little product variation, in terms of uniformity of content of the tablets, hardness, and disintegration and dissolution patterns, within each batch. Wet granulation is usually used to deal with this aspect.

One of the major challenges in this large-scale manufacture of a meloxicam formulation is to formulate a homogenous blend or granule that will remain homogenous during the compression process. Again, wet granulation is usually used to deal with this aspect.

Finally, obtaining a resultant table with optimum disintegration rate characteristics, friability, dissolution patterns and optimum flavour when manufactured on a large-scale is essential.

Thus, there is a need to develop an industrial large-scale process for the preparation of a homogenous meloxicam formulation which deals with these problems which does not involve the additional processing steps involved in wet granulation.

In addition, the properties of the active ingredient itself must be considered. Meloxicam is insoluble in the GI tract. Thus, it would therefore be highly advantageous and most desirable if meloxicam could be rendered palatable without destroying its efficacy and is in a form suitable for immediate release in the GI tract.

Furthermore, it would be most advantageous if a palatable composition containing meloxicam could be prepared in the form of a tablet, pill, granulated product or the like, especially a chewable tablet.

It is therefore an object of this invention to provide palatable, therapeutically effective compositions containing meloxicam, useful for the treatment of arthritis and osteoarthritis in animals.

It is also an object of the present invention to provide methods for preparing compositions containing meloxicam which are palatable for animals, especially dogs.

The present invention aims to address at least some of these problems.

Statement of the Invention

According to a general aspect of the invention, there is provided a process for the preparation of an orally administered palatable unit dose tablet comprising meloxicam involving a pre-lubrication blending step, a lubrication step, followed by a direct compression step.

According to a first aspect of the invention, there is provided a process for the manufacture of an orally administrable palatable unit dose tablet comprising

Meloxicam from 0.1% to 5% by weight;
One or more fillers from 70% to 95% by weight;
One or more disintegrating agents from 1% to 5% by weight;
One or more flavouring agents from 1% to 10% by weight;
One or more stabilizing agents from 1% to 10% by weight;
One or more lubricants from 0.1% to 5% by weight; and
One or more glidants from 0.1% to 5% by weight;

wherein the process comprises the following steps

i) a pre-lubrication blending step comprising mixing the meloxicam, filler, disintegrating agent, stablilizing agent, glidant and flavouring agent in a stepwise fashion to form pre-lubricated granules;

ii) a lubrication step comprising adding the lubricant to the pre-lubricated granules and mixing to form a lubricated mixture

iii) followed by a direct compression step to form an orally administrable palatable unit dose tablet with a friability of less than 1% after 4 minutes and a disintegration time of less than 15 minutes.

According to a second aspect of the invention, the pre-lubrication step may comprise the following steps:

pre-mixing the meloxicam with a first filler and sieving through a 40#mesh to form a meloxicam/first filler mixture;
mixing the remaining ingredients excluding the lubricant and glidant with the meloxicam/first filler mixture and placing in a mixer;
mixing the flavouring agent with the glidant and placing in the mixer;
mixing all ingredients to form pre-lubricated granules.

According to a preferred embodiment of this aspect, the pre-lubrication step comprises

mixing the meloxicam with an approximately equal amount of first filler, adding further first filler and sieving through a 40# mesh sieve to form a sifted mixture, adding further first filler to the sifted mixture and mixing further to form a

meloxicam/first filler mixture;

mixing the remaining first filler, second filler, disintegrating agent and stabiliser with the meloxicam/first filler mixture and placing the resultant mixture in a drum;

mixing the flavouring agent with the glidant to form a flavouring mixture and adding the flavouring mixture to the drum; and

mixing all the ingredients to form pre-lubrication granules

According to a third aspect of the invention, the direct compression step may comprise the following steps:

a. Feeding the lubricated mixture into double polythene lined drums and transferring the lubricated mixture into a hopper;
b. Feeding the lubricated mixture from the hopper into a die cavity of a compression table press;
c. Forming unit dose tablets under direct compression to achieve unit dose tablets with friability of less than 1% after 4 minutes and a disintegration time of less than 15 minutes;
d. Discharging the tablets from the table press into a chute; and
e. Packaging the tablets.

According to a fourth aspect of the invention, there is provided an orally administered palatable unit dose tablet comprising:

meloxicam from 0.1% to 5% by weight

one or more fillers from 70% to 95% by weight

one or more disintegrants from 1% to 5% by weight

one or more flavouring agents from 1% to 10% by weight

one or more stabilizing agents from 1% to 10% by weight;

one or more glidants from 0.1% to 5% by weight; and

one or more lubricants from 0.1% to 5% by weight

wherein the tablet has a friability of less than 1% after 4 minutes and a disintegration time of less than 15 minutes.

Ideally, meloxicam has a particle size wherein at least 90% by weight of the meloxicam particles are less than 10 microns in diameter.

Ideally, the first filler (which may also act as a diluent) has a particle size wherein 100% by weight of the particles are less than 500 microns in diameter, at least 90% by weight of the particles are less than 355 microns in diameter, between 40 to 70% by weight of the particles are less than 150 microns in diameter, and a maximum of 30% of the particles are smaller than 75 microns in diameter. Ideally, lactose, such as lactose DCL 15® is the first filler.

Ideally, an optional second filler (which may also act as a diluent) has an average particle size of approximately 60 microns in diameter. Ideally, silicified microcrystalline cellulose, such as Prosolv SMCC 50®, is the second filler.

Ideally, the stabliser (preferably Sodium citrate) has an average particle size of approximately 150 microns to 700 microns in diameter.

Ideally, the disintegrant (preferably Crospovidone®) has an average particle size of approximately 100 microns to 130 microns in diameter.

Ideally, the glidant (preferably talc) has an average particle size of approximately 10 microns to 150 microns in diameter.

Ideally, the lubricant (preferably Magnesium stearate) has an average particle size of approximately 35 microns to 100 microns in diameter.

Detailed Description of the Invention

In the specification, it will be understood that the term "by weight" refers to the weight of the final composition.

The industrial large-scale manufacture of any drug presents the pharmaceutical manufacturer with many issues to consider. In the large-scale manufacture of a tablet, it is essential that the entire batch being manufactured meets the various criteria set by regulatory legislation. In particular, each tablet within a batch must conform to the active ingredient weight specification, uniformity of content and dissolution specifications and there must be little or no product variation within a batch. Product variation is usually attributed to segregation of the ingredients, in particular the active ingredient, within a batch. This is an unpredictable or random event because pockets of segregated material may end up at the tableting press at irregular intervals. If product variation is found within a batch, this could result in the batch not meeting the required standards and the subsequent wastage of an entire batch. This is expensive and time-consuming and something a pharmaceutical manufacturer will avoid. The present invention is directed to solving these manufacturing problems when making an orally administered unit dose meloxicam tablet on a large-scale.

The present invention is directed to a process for the manufacture of an orally administrable palatable unit does tablet comprising meloxicam wherein the process comprises a pre-lubrication blending step, lubrication step and a direct compression step.

The use of direct compression manufacture which is cost effective and involves the efficient use of manufacturing time. Direct compression i.e. blending of active with highly compressible materials lubricating with magnesium stearate and compressing (instead of wet granulating) the active has advantages when manufacturing on the large-scale. Furthermore, direct compression provides processing advantages over wet granulation processes previously used for manufacturing meloxicam tablets and it also give an advantage in terms of minimizing losses and providing for a more stable end product.

In general terms, the process and formulation according to the invention provides a robust, simple process for producing palatable tablets of good hardness and quality of attributes. Specifically, the process of the invention provides process for the manufacture of an orally administered palatable unit dose meloxicam tablet which has adequate hardness, good dissolution pattern and good uniformity when manufactured on a large-scale.

One of the problems the present invention overcomes is to formulate on a large-scale a homogenous blend of meloxicam that will remain homogenous during the compression process. We have found that one of the critical points is ensuring that the particle size of all ingredients is in the same order of magnitude. By doing this a good flow of the homogeneous blend is maintained and segregation of the ingredients is avoided during compression.

Finally, obtaining the correct dissolution profile, friability and flavour in the resultant tablet is crucial. The specific ingredients used in the present invention and the processing steps ensure that the correct physical parameters are reached.

It will be understood that the tablet produced by this method is a palatable and chewable tablet for veterinary use. The advantage of an orally administered tablet is that the tablet may be administered by an unskilled person. Other forms of administration, such as intravenous administration, are more time consuming and require more expertise.

The tablet comprises several pharmaceutically acceptable carriers and excipients, such as

Fillers (which may also act as diluents) e.g. lactose monohydrate, sucrose, mannitol, maize starch, microcrystalline cellulose, sicilified microcrystalline cellulose (Prosolv®) or calcium hydrogen phosphate;

lubricants e.g. stearic acid, polyethylene glycol, magnesium stearate or colloidal silica;

glidants such as talc;

disintegrants or binding agents e.g. rice, potato or maize starch, sodium starch glycollate or cross-linked N-vinyl-2-pyrrolidone (Crospovidone®)

pH adjustment agents or stabilisers, including sodium or potassium citrate; and

flavouring agents to make the tablet palatable,

Other diluents and excipients having disintegrant, glidant and lubricant properties used in the pharmaceutical field may be used in the process of this invention.

Ideally, lubricants are present in an amount from 0.1% to 5% by weight. The preferred lubricant is magnesium stearate. Other lubricants which may be used in accordance with the invention include magnesium stearate, stearic acid, talcum and bentonites. It is essential in the process of the invention that the magnesium stearate is added at the latest moment possible to ensure it has the least amount of time in contact with the active ingredient. Magnesium stearate is hydrophobic and affects the solubility and dissolution profile of the active ingredient. The process of the present invention aims to minimise the contact time between the blended ingredients and the magnesium stearate.

Ideally, glidants are present in an amount from 0.1% to 5% by weight. The preferred lubricant is talc.

Ideally, the flavouring agent is present in an amount from 0.1% to 10% by weight. The flavouring agents are commercially available synthetic flavourings. Preferred flavouring agents are meat flavours. Meat flavours are commercially available as additives for pet feed. Other savoury or sweet flavours may be used.

Ideally, the ph Adjustment or stabilizing agents are present from 1% to 10% by weight. Ideally, sodium citrate is used.

Ideally, a disintegrating agent (or disintegrant) is present up to an amount of 5%. Ideally, Crospovidone® is used.

Ideally, fillers/diluents are present in an amount up to 95% by weight. Preferably, a first and second filler are used, in which the first filler is a lactose monohydrate and the second filler is silicified microcrystalline cellulose (e.g. Prosolv SMCC®), or vice versa. When both fillers are used, they both add up to the percentage outlined above and both fillers satisfy the size requirement outlined below.

Silicified microcrystalline cellulose may be used which acts as a filler as well as a binding agent/diluent has good compactability and flow properties. In one embodiment of the invention, silicified microcrystalline cellulose comprising microcrystalline cellulose and colloidal silicon dioxide is used as the filler. It may also have glidant properties. For

example, colloidal silicon dioxide may act as a glidant to improve flow characteristics of the tableting powder.

The silicified microcrystalline cellulose is generally of a specific particle size wherein at least 90% of the silicified microcrystalline cellulose particles are less than approximately 140 microns in diameter. Silicified Microcrystalline Cellulose, PROSOLV™, may be used which is a combination of 98% microcrystalline cellulose USP/NF, BP, Ph.Eur., JP and 2% colloidal silicon dioxide USP/NF, BP, Ph. Eur., JP. Other potentially suitable dispersing/disintegrant agents include colloidal silicon dioxide such as that sold under Aerosil 200® and/or a non-ionic surfactant such as a polyoxyethylene derivative of a sorbitan ester marketed as Polysorbate 20®.

The narrow particle size distribution for these excipients ensures a low tablet weight variation and good uniformity of the drug. Particle size for each of there ingredients will be expanded on below.

The resultant tablet has a friability of less than 1% after 4 minutes and a disintegration time of less than 15 minutes.

In order to obtain the advantage of the present invention, all the ingredients should be in same particle size range to obtain a homogenous blended powder. Furthermore, in addition powders are screened/sieved during production to eliminate any agglomerated particles.

A typical particle size (diameter) range of a formulation according to the invention follows:

Meloxicam	90% or more < 10µm
Filler (Lactose DCL 15®)	100% < 500µm / 90% <355µm / 40 to 70% <150µm / 30% <75µm
Filler (Prosolv SMCC 50®)	avr. particle size of approx. 60 µm
Disintegrant (Crospovidone®)	avr. particle size approx.100 to 130 µm

Stabliser (Sodium citrate)	avr. particle size approx. 150 to 70 µm
Lubricant (Magnesium Stearate)	avr. particle size approx. 35 to 100 µm
Glidant (talc)	avr. particle size of approx. 10 to 150 µm

The particle size of the active ingredient is an essential requirement for this invention and significantly improves the manufacture of a uniform tablet with the required dissolution and disintegration parameters.

The particle size of the active ingredient provides for good bioavailability of the active ingredient when administered to a patient. Furthermore, the particle size of active is important for good dissolution and bioavailability.

In addition, it is important to ensure that the particle sizes of all excipients are in same range as active to achieve for good homogeneity of blend which is maintained during compression.

At each step during the pre-lubrication and lubrication steps, the active ingredient and the excipients are sieved to break down agglomerates that may have formed in the excipients. For example, a 20# mesh may be used to break down agglomerates bigger than approximately 800 to 900 microns, preferably 850 microns. A 40# mesh may be used to break down agglomerates bigger than approximately 400 microns, preferably 400 microns.

Pre-lubrication Blending

According to one preferred embodiment, the sieved ingredients (excluding the lubricant) are mixed with the Meloxicam in a stepwise fashion, sieved where necessary and added to a blender for final mixing to obtained pre-lubricated granules. This is the pre-lubrication step.

Ideally, the Meloxicam is mixed with the first filler, preferably lactose, in a stepwise fashion. The mixture is ideally sieved to a 40# mesh.

This is then mixed with the remaining filler, second filler, stabiliser and disintegrant.

The flavouring agent is then mixed with the talc to form a flavouring mixture.

All the above ingredients are loaded into a drum blender and mixed for approximately 20-40 minutes, depending on the speed of the drum blender.

Blending is carried out to achieve uniformity of the active ingredient in the blend. This is generally when the homogeneity of the blend is 90 to 110% of the expected active content with a relative standard deviation (RSD) of 5% or less. Once uniformity has been tested and the desired uniformity has been reached, blending is stopped. Ideally, blending at this step occurs for 10 to 30 minutes, preferably 20 minutes.

It will be understood that this pre-lubrication blending step may be carried out in different ways, all involving the stepwise addition of excipients (excluding the lubricant). Such methods are outlined in the Examples.

For example, in an alternative pre-lubrication step, the sieved ingredients (excluding the lubricant) are mixed in a blender after sieving in a step wise fashion wherein Meloxicam is added to part of the other excipients, mixed and added to the remainder of the excipients. This is the pre-lubrication step. The mixture is sieved to a 40# mesh and mixed with the remainder of the other excipients. The flavouring agent is then added to the mixture, and sieved through a 20# mesh. The mixture is then loaded into a drum blender and mixed for approximately 20-40 minutes. Such an alternative method comprises the following steps

i) sieving the fillers, disintegrating agent, glidant and stabilizing agent through a 20 mesh and mixing;
ii) adding the Meloxicam to the mixed ingredients from (i);
iii) sieving the ingredients from (ii) through a 40 mesh;
iv) adding the flavouring agent; and
v) mixing, preferably for approximately 20 minutes, to form pre-lubricated granules.

Lubrication

The lubricant, preferably magnesium stearate, is then sieved to remove lumps/agglomeration of powders in the powder material. Again, ideally a 20# mesh is used to break down particles with an average particle size of greater than approximately 800 to 900 microns, preferably 850 microns. Typically, a Russell Sieve is used.

The sieved magnesium stearate is then added to the blended ingredients and blended. This is the lubrication step.

Typically, blending post-lubrication is only needed for a short time, for example three to ten minutes, preferably three to five minutes. This ensures that the magnesium stearate and active ingredient are in contact for the minimum time necessary. Blending is stopped once uniformity of the ingredients in the mix has been achieved. This is generally when 90 to 110% of the active ingredient is blended with a relative standard deviation (RSD) of 5% or less.

Tabletting

Post lubrication, the blended mixture, which is also known as the tableting powder, is transferred to containers. Suitable containers include double lined polyethylene bags in High Density Polyethylene container. These drums are lined in order to ensure that contamination of the mixture is avoided and protect the product from moisture etc.

The tableting powder is then transferred to a hopper and loaded into the punches of a tableting press. Ideally, a rotary tablet compression machine or table/tableting press is used.

According to one embodiment the hopper is the part of tabletting machine. Once the blend is loaded into the hopper, the blend goes into Filomatic® force-feeder of the machine by gravity and then goes into die cavity of the compression machine. The Filomatic® force feeder is the part of the tabletting machine which provides uniformity of unit dose tablets.

The tableting press is set up with upper and lower punches and dies of a specific diameter depending on the tablet strength being compressed.

The pressure applied in the tableting press depends on the tablet being manufactured, for example tablets may be manufactured with 0.25mg, 0.5mg, 1.0mg, 2.5mg and 5mg of active ingredient. Punches of different diameter are used depending on the tablet strength and associated weight of the tablet to be compressed. Generally, compression forces applied are in the range of 1 to 10 KiloNewtons.

Separate tooling of defined diameter is used for each strength (e.g. 10.5 FBE with break line for 2.5mg tablets and 7.5 FBE with break line for 1.0mg tablets) to product a tablet with good hardness, disintegration and friability characteristics and with a thickness that produces an aesthetically good tablet.

It is desirable to obtain tablets with a friability of less than 1% after 100 revolutions or 4 minutes and a disintegration time of less than 15 minutes with appropriate hardness and thickness.

After the tablets are punched, they are collected in suitable containers for storage or packaged directly.

Preferably, the containers used according to this invention are double lined polyethylene bags in High Density Polyethylene containers. They are double lined in order to provide the requisite contamination-free conditions.

The tablets are packaged in blister packs composed of PVC/PVDC 250/60 film and 20 um aluminium foil. This is the packaging for the market blister in cartons.

According to the present invention the composition is in the form of a tablet, preferably a chewable tablet.

Tablets according to this invention may be right circular cylinders, the end surfaces of which may be flat or convex and the level edged. Said tablets may have lines or break-marks and may bear a symbol or other markings.

The tablets according to the present invention also should have an appropriate strength. An appropriate strength is defined as exceeding 100 N (Newton). Said tablets have a thickness of about 4.5 mm.

Ideally, the 1mg tablets have a thickness range 3.4 to 3.8mm and the 2.5mg tablets have thickness range 4.4 to 4.8mm.

The tablets of the present invention are preferable packaged in impermeable package, e.g. Tristar, which is a laminate van polyvinyl chloride, polyethylene and polyvinylidene chloride.

The process of the present invention provides an advantage in terms of manufacture of a tablet on an industrial scale. The process used involves fewer manufacturing steps than conventional granulation techniques that would normally be used in the manufacture of such orally administered unit dose tablets.

According to one embodiment, the tablets made according to the present invention are packaged after production. They may be packaged in blisters made of PVC/PVdC and hard temper aluminium foil or high density polyethylene twist-off plastic containers with white polypropylene twist-off caps. The orally administered unit dose may be in the form of tablets or capsule.

According to another embodiment of the invention, the tablets are delivered to a container and stored in contamination-free conditions prior to final packaging for the market.

The invention further provides an orally administered unit dose tablet as prepared by the process.

The invention further provides an orally administered unit dose tablet for use in treating arthritis and osteoarthritis for veterinary use.

Figures and Example

The invention is not limited to the embodiments described above but may be varied within the scope of the claims.

The invention will now be described by reference to the following non-limiting examples and figures.

Figure 1 shows a flowchart for the manufacture of a unit dose meloxicam tablet.

Figure 2 shows a flowchart outlining an alternative method for the manufacture of a unit dose (1mg) meloxicam tablet.

As shown in Figure 1, the general method involved the steps of dispensing the excipient ingredients (excluding the lubricant) of an appropriate particulate size and set ratio. These ingredients and the active ingredient are then sieved in a step wise fashion and mixed in a blender. This is the pre-lubrication step.

A set ratio of magnesium stearate (the lubricant) to active ingredient is sieved before adding it to the blended mixture. A further mixing step is undertaken. This is the lubrication step.

The resultant blended ingredients are optionally transferred to a container and then transferred to a hopper.

The tableting press is filled with the blended ingredients from the hopper. The tableting press is fitted with dies and upper and lower punches of a specific diameter depending on the tablet being produced.

The tableting powder is compressed to achieve tablets of set characteristics and then transferred to a container, optionally stored and then packaged.

As shown in Figure 2, the active ingredient meloxicam is first mixed stepwise with increasing amounts of the first filler, lactose. Ideally, the mixture is passed through a 40# mesh sieve during this process. This stage results in the formation of a meloxicam/first filler (lactose) mixture.

The meloxicam/first filler (lactose) mixture and the pre-lubrication pre-mix comprising second filler (Prosolv), sodium citrate (stabilizer), crospovidone (disintegrant) and the remaining quantity of first filler (lactose) is placed in a drum blender.

The flavour mixture is then formulated by mixing and sifting the flavouring agent, such as pork flavour, with the glidant (talc) and a small amount of the pre-lubrication pre-mix.

The meloxicam/first filler (lactose mixture), the flavour mixture and the pre-lubrication pre-mix are mixed in the drum blender to form a pre-lubrication mixture. Ideally mixing takes place for 20 minutes, however, this depends on what setting is used.

The lubricant, magnesium stearate, is sieved, ideally through a 20#mesh sieve, and added to the pre-lubrication mixture to form a lubricated mixture.

The lubricated mixture then undergoes compression as described above to form unit dose tablets.

Example 1: Manufacturing Process - Meloxicam Chewable/PalatableTablets

Equipment Required:

Sieve with 20# screen mesh to screen agglomerated particles greater than approximately 800 to 900 microns in diameter

Sieve with 40# screen mesh to screen agglomerated particles greater than approximately 400 to 500 microns in diameter

Blender - Double cone blender or drum tumbler may be used

Compression machine – Rotary Tablet Compression Machine

Ingredients:

Ingredients		mg/tab	Quantity (grams)	% by weight in formulation
Meloxicam	API	2.5	38.5	0.556
Lactose DCL®	Filler/Diluent	270	4.158	60.00
Prosolv SMCC 50®	Filler/Diluent	135	2.079	30.00
Sodium citrate PhEur, BP	pH adjustment/ stabilizing agent	9	138.6	2.00
Crospovidone® (PolyplasdoneXL) PhEur	Disintegrating Agent	11	169.4	2.444
Talc PhEur	Glidant	9	138.6	2.00
Mg stearate BP/ PhEur/USP	Lubricant	4.5	69.3	1.0
Pork flavour (manufactured by Givaudan 613045E)	Synthetic Flavour	9	138.6	2.00
Total		450	6.93 kg	100.00

The above table outlines the ingredients used in a 2.5mg meloxicam tablet. 1mg (i.e. comprising 1mg of active ingredient) tablets may also be manufactured and the proportion of each ingredient in the above table is then altered accordingly.

Example 1 Method:

The following general method was used in the manufacture of a unit dose tablet according to the invention. The method below relates to the manufacture of both a 2.5mg and 1mg tablet.

Pre-Lubrication Blending

1) Lactose DCL –15®, Sodium citrate, Crospovidone®, Prosolv® and talc were sifted through a 20 mesh;
2) The mixture from step 1 was mixed with approx. 40g to Meloxicam (API);
3) A further 80g of mixture from step-1 was added to the mixture of step 2 and mixed;
4) A further approx.160g. of mixture from step-1 was added to the mixture from step 3 and mixed;
5) A further approx.300g of mixture from step-1 was added to the mixture from step 4 and mixed;
6) The mixture from step 5 was passed through a 40 mesh and another 600g.of mixture from step1 was added and mixed;.
7) The remaining of mixture from step 1 was added to the mixture from step 6 and mixed well;
8) Approximately 150g of the powder blend of step 7 was added to the pork flavour and mixed; it was then sifted through a 20 mesh and the sieve was rinsed using powder blend of step 7; this flavour mixed powder was added to the powder blend of step 7 and mixed;
9) The powder mixture from step 8 and step 7 was loaded into a drum and mixed for approx. 20 min;
10) A sample was removed to test content uniformity and assay (pre-lubricated granules - sample)

Lubrication

11) Magnesium stearate was sifted and added to the mixture of step 8 and mixed;
12) A sample of lubricated granules was removed for analysis;

Compression

13) The resultant lubricated blend was compressed using 10.5mm FBE with break line punches with deep break line on tablet mini-press; and the compression parameters were recorded:

Ideal compression parameters follow for the 2.5mg tablet:

Parameter	**Meloxicam 2.5mg.**
Appearance	Off white to pale yellow plain round FFBE with break line on one side
Av.weight	450mg. (448 – 455 mg/tab.)
Hardness	75 – 95 N
Disintegration time	25-30 sec.
Friability	0.12%
Diameter	10.52 – 10.56 mm
Thickness	4.4-4.8mm

The above method was used in the manufacture of both 1mg and 2.5mg tablets, although it will be appreciated that other tablets could be contemplated.

Stability Data Results

Meloxicam tablets (both 1mg and 2.5mg) were subjected to various stability tests under different conditions. Results are shown below.

Table 1 : Meloxicam Chewable Tablets 1mg – Stability Results 25C/60%R

Meloxicam Chewable tablets 1.0 mg	Strength :1.0 mg/tablet		
Storage condition: 25C/60%RH	Intervals : 0,3,6,9,12,18,24,36 mths		
Test	**Specification**	**Initial**	**3 mths**
Appearance of Product	Off white to pale yellow coloured, flat surface bevelled edged tablets plain on one side and break line on the other side.	Complies	Complies
Condition of Packaging	Packaging Intact	Complies	Complies
Identification pork flavour *	Positive for its odour	Complies	NP
Identification (Active) *	The retention time of the principal peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay	Complies	NP
Average Weight	180 mg ± 5% (171.0 mg - 189.0 mg)	179.90 mg	181.06 mg
Uniformity of weight *	Not more than 2 Tablets should deviate by more than 7.5% and none by more than 15% from the average weight, when tested on 20 tablets.	Complies	NP
Uniformity of dosage units (Content uniformity) *	Conforms to Ph.Eur	Complies AV = 5.4	NP
Uniformity of dosage units (Content uniformity of half tablet) *	Conforms to Ph.Eur	Complies AV = 9.77	NP
Hardness	Record	37N	33N
Friability	Not more than 1% after 4 minutes	0.13%	0.07%
Disintegration time	Not more than 15 min	0.23 min	0.17min
Water content	Record	4.69%	5.34%
Assay Active	Meloxicam 1.0 mg/tab ± 5% i.e. 0.95 mg/tab – 1.05 mg/tab	0.99 mg	0.99 mg
Dissolution	NLT 80%(Q+5%) after 30minutes	93.70%	90.90%
	Range :	90.8-98.2%	89.6-92.4%
Related substance (Report all unknown impurities >0.05%)	Impurity A : ≤ 0.5% (RRT)	ND	ND
	Impurity B : ≤ 0.5% (RRT)	0.010% (0.45)	0.010%(0.44)
	Impurity C : ≤ 0.5% (RRT)	0.004% (1.74)	0.005%(1.73)
	Individual Unknown Impurity : ≤ 1%(RRT)	ND	< 0.05%
	Total Impurities : ≤ 3%	0.014%	0.015%
Microbiology**	Conforms to Ph.Eur	Complies	NP

*To test at initial time point only ** To be carried out initially and at 36 months
NP : Not Performed ND : Not Detected NLT Not Less Than

Table 2 : Meloxicam Chewable Tablets 1mg – Stability Results 30C/65%RH

Meloxicam Chewable tablets 1.0 mg	Strength :1.0 mg/tablet
Storage condition: 30C/65%RH	Intervals : 0,3,6,9 & 12, mths

Test	Specification	Initial
Appearance of Product	Off white to pale yellow coloured, flat surface bevelled edged tablets plain on one side and break line on the other side.	Complies
Condition of Packaging	Packaging Intact	Complies
Identification pork flavour *	Positive for its odour	Complies
Identification (Active) *	The retention time of the principal peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay	Complies
Average Weight	180 mg ± 5% (171.0 mg - 189.0 mg)	179.90 mg
Uniformity of weight *	Not more than 2 Tablets should deviate by more than 7.5% and none by more than 15% from the average weight, when tested on 20 tablets.	Complies
Uniformity of dosage units (Content uniformity) *	Conforms to Ph.Eur	Complies AV = 5.4
Uniformity of dosage units (Content uniformity of half tablet) *	Conforms to Ph.Eur	Complies AV = 9.77
Hardness	Record	37.4 N
Friability	Not more than 1% after 4 minutes	0.13%
Disintegration time	Not more than 15 min	14Sec
Water content	Record	4.69%
Assay Active	Meloxicam 1.0 mg/tab ± 5% i.e. 0.95 mg/tab – 1.05 mg/tab	0.99 mg
Related substance (Report all unknown impurities >0.05%)	Impurity A : ≤ 0.5% (RRT)	ND
	Impurity B : ≤ 0.5% (RRT)	0.010% (0.45)
	Impurity C : ≤ 0.5% (RRT)	0.004% (1.74)
	Total Unknown Impurity : ≤ 1%(RRT)	ND
	Total Impurities : ≤ 3%	0.014%
Microbiology	Conforms to Ph.Eur	Complies

*To test at initial time point only
NP : Not Performed ND : Not Detected NLT Not Less Than

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Table 3 : Meloxicam Chewable Tablets 1mg – Stability Results 40C/75%RH

Meloxicam Chewable tablets 1.0 mg	Strength :1.0 mg/tablet
Storage condition: 40C/75%RH	Intervals : 0,1,2,3 & 6, mths

Test	Specification	time interval			
		Initial	1 mths	2 mths	3 mths
Appearance of Product	Off white to pale yellow coloured, flat surface bevelled edged tablets plain on one side and break line on the other side.	Complies	Complies	Complies	Complies
Condition of Packaging	Packaging Intact	Complies	Complies	Complies	Complies
Identification pork flavour *	Positive for its odour	Complies	NP	NP	NP
Identification (Active) *	The retention time of the principal peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay	Complies	NP	NP	NP
Average Weight	180 mg ± 5% (171.0 mg - 189.0 mg)	179.90 mg	182.01mg	182.33mg	182.18 mg
Uniformity of weight *	Not more than 2 Tablets should deviate by more than 7.5% and none by more than 15% from the average weight, when tested on 20 tablets.	Complies	NP	NP	NP
Uniformity of dosage units (Content uniformity) *	Conforms to Ph.Eur	Complies AV = 5.4	NP	NP	NP
Uniformity of dosage units (Content uniformity of half tablet) *	Conforms to Ph.Eur	Complies AV = 9.77	NP	NP	NP
Hardness	Record	37N	32N	30N	31N
Friability	Not more than 1% after 4 minutes	0.13%	0.10%	0.74%	0.14%
Disintegration time	Not more than 15 min	0.23 min	0.37min	0.40 min	0.13min
Water content	Record	4.69%	4.86%	5.90%	5.51%
Assay Active	Meloxicam 1.0 mg/tab ± 5% i.e. 0.95 mg/tab – 1.05 mg/tab	0.99 mg	0.98 mg	0.98 mg	0.99 mg
Dissolution	NLT 80%(Q+5%) after 30minutes	93.70%	88.10%	85.10%	87.10%
	Range :	90.8 - 98.2%	85.3 - 89.9%	84.3 - 86.2%	85.0- 89.0%
Related substance (Report all unknown impurities >0.05%)	Impurity A : ≤ 0.5% (RRT)	ND	ND	ND	ND
	Impurity B : ≤ 0.5% (RRT)	0.010% (0.45)	0.020%(0.45)	0.067%(0.44)	0.044%(0.44)
	Impurity C : ≤ 0.5% (RRT)	0.004% (1.74)	0.004% (1.73)	ND	0.005%(1.71)
	Individual Unknown Impurity : ≤ 1%(RRT)	ND	ND	ND	< 0.05%
	Total Impurities : ≤ 3%	0.014%	0.024%	0.067%	0.049%
Microbiology	Conforms to Ph.Eur	Complies	NP	NP	NP

*To test at initial time point only NP : Not Performed ND : Not Detected NLT Not Less Than

Table 4 : Meloxicam Chewable Tablets 2.5mg – Stability Results 25C/60%RH

:Meloxicam Chewable tablets 2.5 mg	Strength :2.5 mg/tablet
Storage condition: 25C/60%RH	Intervals : 0,3,6,9,12,18,24,36 mths

Test	Specification	Initial	3 mths
Appearance of Product	Off white to pale yellow coloured, flat surface edged tablets plain on one side and break line on the other side.	Complies	Complies
Condition of Packaging	Packaging Intact	Complies	Complies
Identification pork flavour *	Positive for its odour	Complies	NP
Identification (Active) *	The retention time of the principal peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay	Complies	NP
Average Weight	450 mg ± 5% (427.5 mg - 472.5 mg)	450.80 mg	449.92 mg
Uniformity of weight *	Not more than 2 Tablets should deviate by more than 7.5% and none by more than 15% from the average weight, when tested on 20 tablets.	Complies	NP
Uniformity of dosage units (Content uniformity) *	Conforms to Ph.Eur	Complies AV = 3.1	NP
Uniformity of dosage units (Content uniformity of half tablet) *	Conforms to Ph.Eur	Complies AV = 4.6	NP
Hardness	Record	75N	73N
Friability	Not more than 1% after 4 minutes	0.003%	0.13%
Disintegration time	Not more than 15 min	0.48 min	0.30min
Water content	Record	4.86%	5.16%
Assay Active	Meloxicam 2.5 mg/tab ± 5% i.e. 2.375 mg/tab – 2.625 mg/tab	2.48 mg	2.50 mg
Dissolution	NLT 80%(Q+5%) after 30minutes	83.40%	85.50%
	Range :	80.9 - 85.4%	81.9-88.3
Related substance (Report all unknown impurities >0.05%)	Impurity A : ≤ 0.5% (RRT)	ND	ND
	Impurity B : ≤ 0.5% (RRT)	0.014% (0.45)	0.013%(0.44)
	Impurity C : ≤ 0.5% (RRT)	0.004% (1.74)	0.005%(1.72)
	Individual Unknown Impurity : ≤ 1%(RRT)	ND	< 0.05%
	Total Impurities : ≤ 3%	0.018%	0.018%
Microbiology**	Conforms to Ph.Eur	Complies	NP

*To test at initial time point only ** To be carried out initially and at 36 months
NP : Not Performed ND : Not Detected NLT Not Less Than

Table 5 : Meloxicam Chewable Tablets 2.5mg – Stability Results 30C/65%RH

Meloxicam Chewable tablets 2.5 mg	Strength :2.5 mg/tablet
Storage condition: 30C/65%RH	Intervals : 0,3,6,9 & 12, mths

Test	Specification	Initial
Appearance of Product	Off white to pale yellow coloured, flat surface edged tablets plain on one side and break line on the other side.	Complies
Condition of Packaging	Packaging Intact	Complies
Identification pork flavour *	Positive for its odour	Complies
Identification (Active) *	The retention time of the principal peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay	Complies
Average Weight	450 mg ± 5% (427.5 mg - 472.5 mg)	450.80 mg
Uniformity of weight *	Not more than 2 Tablets should deviate by more than 7.5% and none by more than 15% from the average weight, when tested on 20 tablets.	Complies
Uniformity of dosage units (Content uniformity) *	Conforms to Ph.Eur	Complies AV = 3.1
Uniformity of dosage units (Content uniformity of half tablet) *	Conforms to Ph.Eur	Complies AV = 4.6
Hardness	Record	74.7 N
Friability	Not more than 1% after 4 minutes	0.003%
Disintegration time	Not more than 15 min	29 Sec
Water content	Record	4.86%
Assay Active	Meloxicam 2.5 mg/tab ± 5% i.e. 2.375 mg/tab – 2.625 mg/tab	2.48 mg
Dissolution	NLT 80%(Q+5%) after 30minutes	
	Range :	
Related substance (Report all unknown impurities >0.05%)	Impurity A : ≤ 0.5% (RRT)	ND
	Impurity B : ≤ 0.5% (RRT)	0.014% (0.45)
	Impurity C : ≤ 0.5% (RRT)	0.004% (1.74)
	Individual Unknown Impurity : ≤ 1%(RRT)	ND
	Total Impurities : ≤ 3%	0.018%
Microbiology**	Conforms to Ph.Eur	Complies

*To test at initial time point only ** To be carried out initially and at 36 months
NP : Not Performed ND : Not Detected NLT Not Less Than

Table 6 : Meloxicam Chewable Tablets 2.5mg – Stability Results 40C/75%RH

Meloxicam Chewable tablets 2.5 mg	Strength :2.5 mg/tablet
Storage condition: 40C/75%RH	Intervals : 0,1,2,3 & 6, mths

Test	Specification	time interval			
		Initial	1 mths	2 mths	3 mths
Appearance of Product	Off white to pale yellow coloured, flat surface bevelled edged tablets plain on one side and break line on the other side.	Complies	Complies	Complies	Complies
Condition of Packaging	Packaging Intact	Complies	Complies	Complies	Complies
Identification pork flavour *	Positive for its odour	Complies	NP	NP	NP
Identification (Active) *	The retention time of the principal peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay	Complies	NP	NP	NP
Average Weight	450 mg ± 5% (427.5 mg - 472.5 mg)	450.80 mg	454.69 mg	455.13 mg	455.90 mg
Uniformity of weight *	Not more than 2 Tablets should deviate by more than 7.5% and none by more than 15% from the average weight, when tested on 20 tablets.	Complies	NP	NP	NP
Uniformity of dosage units (Content uniformity) *	Conforms to Ph.Eur	Complies AV = 3.1	NP	NP	NP
Uniformity of dosage units (Content uniformity of half tablet) *	Conforms to Ph.Eur	Complies AV = 4.6	NP	NP	NP
Hardness	Record	75N	70N	69N	71N
Friability	Not more than 1% after 4 minutes	0.003%	0.48%	0.40%	0.29%
Disintegration time	Not more than 15 min	0.48 min	0.57min	0.73min	0.30min
Water content	Record	4.86%	5.40%	5.74%	5.16%
Assay Active	Meloxicam 2.5 mg/tab ± 5% i.e. 2.375 mg/tab – 2.625 mg/tab	2.48 mg	2.47 mg	2.47mg	2.51mg
Dissolution	NLT 80%(Q+5%) after 30minutes	83.40%	87.10%	83.70%	82.40%
	Range :	80.9 - 85.4%	85.6 - 88.5%	82.2 - 85%	80.3- 84.0%

Table 6 (cont'd) : Meloxicam Chewable Tablets 2.5mg – Stability Results 40C/75%RH

Meloxicam Chewable tablets 2.5 mg		Strength :2.5 mg/tablet			
Storage condition: 40C/75%RH		Intervals : 0,1,2,3 & 6, mths			
Test	Specification	time interval			
		Initial	**1 mths**	**2 mths**	**3 mths**
Related substance (Report all unknown impurities >0.05%)	Impurity A : ≤ 0.5% (RRT)	ND	ND	ND	ND
	Impurity B : ≤ 0.5% (RRT)	0.014% (0.45)	0.015% (0.45)	0.059% (0.44)	0.060%(0.44)
	Impurity C : ≤ 0.5% (RRT)	0.004% (1.74)	0.004% (1.73)	ND	0.005%(1.74)
	Individual Unknown Impurity : ≤ 1%(RRT)	ND	0.147%(2.12)	0.080% (0.36)	< 0.05%
	Total Impurities : ≤ 3%	0.018%	0.166%	0.139%	0.065%
Microbiology**	Conforms to Ph.Eur	Complies	NP	NP	NP
*To test at initial time point only ** To be carried out initially and at 36 months NP : Not Performed ND : Not Detected NLT Not Less Than					

Example 2 : Additional Stability Testing Results

1mg meloxicam tablets were made in accordance with the method of Example 1 and subjected to stability testing over a 12 month period under 2 different storage conditions.

Table 7

1 mg Meloxicam	Blister PVC/PVdC (250.60)	Temp: 25°C/60%RH

Test	Specification	Initial	3mths	6mths	9mths	12mths
Appearance	Off white to pale yellow coloured, flat surface bevelled edged tablets with a break line on one side	Conforms	Conforms	Conforms	Conforms	Conforms
Condition of Packaging	Packaging intact	Conforms	Conforms	Conforms	Conforms	Conforms
Disintegration	Conforms to Ph. Eur	0.23m	0.13m	0.13m	0.68m	0.33m
Dissolution Meloxicam	NLT 80% dissolved after 60 minutes	93.7%	89.3%	87.7%	88.7%	90.5%
Active Assay Meloxicam	1 mg/tablet ± 5% (0.96 – 1.05 mg/tablet)	0.99mg	1.00mg	0.99mg	0.99mg	0.99mg
Related Substances	Impurity A ≤ 1% Impurity B ≤ 1% Impurity C ≤ 1% Individual Unknown Impurities ≤ 1% Total Impurities ≤ 6%	ND 0.010% 0.004% Conforms 0.014%	ND 0.011% 0.005% Conforms 0.016%	ND 0.057% 0.005% Conforms 0.124%	ND 0.041% 0.005% Conforms 0.046%	ND 0.056% 0.005% Conforms 0.061%
Microbial Quality*	Conforms to Ph. Eur	Conforms	NP	NP	NP	NP

*To be carried out initially and at 36 mths/D.O.M. Date of Manufacture/NP Not Performed/ND Not detected

Table 8

1 mg Meloxicam	Blister PVC/PVdC (250.60)	Temp: 40°C/75%RH

Test	Specification	Initial	3mths	6mths
Appearance	Off white to pale yellow coloured, flat surface bevelled edged tablets with a break line on one side	Conforms	Conforms	Conforms
Condition of Packaging	Packaging intact	Conforms	Conforms	Conforms
Disintegration	Conforms to Ph. Eur	0.23m	0.08m	0.22m
Dissolution Meloxicam	NLT 80% dissolved after 60 minutes	93.7%	88.2%	91.6%
Active Assay Meloxicam	1 mg/tablet ± 5% (0.96 – 1.05 mg/tablet)	0.99mg	0.99mg	0.99mg
Related Substances	Impurity A ≤ 1% Impurity B ≤ 1% Impurity C ≤ 1% Individual Unknown Impurities ≤ 1% Total Impurities ≤ 6%	ND 0.010% 0.004% Conforms 0.014%	ND 0.046% 0.005% Conforms 0.051%	ND 0.081% 0.005% Conforms 0.238%
Microbial Quality*	Conforms to Ph. Eur	Conforms	NP	NP

*To be carried out initially and at 36 mths. D.O.M. Date of Manufacture NP Not Performed ND Not detected

Example 3 : Additional Stability Testing Results

2.5mg meloxicam tablets were made in accordance with the method of Example 1 and subjected to stability testing over a 12 month period under 2 different storage conditions.

Table 9

2.5 mg Meloxicam	Blister PVC/PVdC (250.60)	Temp: 25°C/60%RH

Test	Specification	Initial	3mths	6mths	9mths	12mths
Appearance	Off white to pale yellow coloured, flat surface bevelled edged tablets with a break line on one side	Conforms	Conforms	Conforms	Conforms	Conforms
Condition of Packaging	Packaging intact	Conforms	Conforms	Conforms	Conforms	Conforms
Disintegration	Conforms to Ph. Eur	0.48m	0.37m	0.33m	0.85m	0.33m
Dissolution Meloxicam	NLT 80% dissolved after 60 minutes	83.4%	87.0%	90.6%	83.2%	86.3%
Active Assay Meloxicam	2.5 mg/tablet ± 5% (2.275 – 2.625 mg/tablet)	2.48mg	2.53mg	2.46mg	2.47mg	2.52mg
Related Substances	Impurity A ≤ 1% Impurity B ≤ 1% Impurity C ≤ 1% Individual Unknown Impurities ≤ 1% Total Impurities ≤ 6%	ND 0.014% 0.004% Conforms 0.018%	ND 0.014% 0.005% Conforms 0.019%	ND 0.030% 0.005% Conforms 0.035%	ND 0.032% 0.005% Conforms 0.037%	ND 0.054% 0.005% Conforms 0.059%
Microbial Quality*	Conforms to Ph. Eur	Conforms	NP	NP	NP	NP

*To be carried out initially and at 36 mths. D.O.M. Date of Manufacture NP Not Performed ND Not detected

Table 10

2.5 mg Meloxicam	Blister PVC/PVdC (250.60)	Temp: 40°C/75%RH

Test	Specification	Initial	3mths	6mths
Appearance	Off white to pale yellow coloured, flat surface bevelled edged tablets with a break line on one side	Conforms	Conforms	Conforms
Condition of Packaging	Packaging intact	Conforms	Conforms	Conforms
Disintegration	Conforms to Ph. Eur	0.48m	0.27m	0.25m
Dissolution Meloxicam	NLT 80% dissolved after 60 minutes	83.4%	82.1%	88.5%
Active Assay Meloxicam	2.5 mg/tablet ± 5% (2.275 – 2.625 mg/tablet)	2.48mg	2.46mg	2.46mg
Related Substances	Impurity A ≤ 1% Impurity B ≤ 1% Impurity C ≤ 1% Individual Unknown Impurities ≤ 1% Total Impurities ≤ 6%	ND 0.014% 0.004% Conforms 0.018%	ND 0.060% 0.005% Conforms 0.065%	ND 0.080% 0.005% Conforms 0.085%
Microbial Quality*	Conforms to Ph. Eur	Conforms	NP	NP

*To be carried out initially and at 36 mths. D.O.M. Date of Manufacture NP Not Performed ND Not detected

Example 4

Pharmacokinetics – Meloxicam Tablet

The pharmacokinetics of the Meloxicam Tablet made in accordance with Example 1 and the reference product, Metacam® Tablet, were compared in the target species dogs, by way of a bioequivalence study. This bioequivalence study was performed using Meloxicam Tablet containing 2.5 mg Meloxicam.

Bioequivalence Study

The bioequivalence study design was a two-way, single dose crossover blood bioequivalence conducted by the applicant to determine the plasma concentrations in dogs following oral administration with the test item Meloxicam and the reference product (Metacam Tablet). The study was performed in accordance with the OECD principles of Good Laboratory Practice.

In this study twenty-four beagle dogs were allocated into two groups of 12 dogs with 6 male and 6 female in each group. The dogs were aged between 5 and 6 months. The male dogs weighed between 8.8 and 10.4 kg while the female dogs weighed between 6.8 and 9.0Kg at the onset of treatment. Animals were randomised manually to their respective study treatment groups based on their body weight one week prior to the start of the study.

Following an acclimatisation period of seven days each animal was administered orally with either the test or the reference item (as per group allocation). The products were given orally by placing the tablet as close as possible to the oesophagus and pouring 10 ml of drinking water into the dog's mouth using a volumetric syringe.

The target dose rate was 0.2 mg/kg of Meloxicam per bodyweight of animal. Serial blood samples were taken from the v. cephalica antebrachii prior to treatment and at the following time points following treatment, 1h, 3h, 5h, 6h, 7h, 7.5h, 8h, 8.5h, 9h, 10h, 12h, 24h, 36h, 48h, 72 h, 96 h and 120 h after treatment.

The study was divided into two individual phases with a fourteen-day washout between the two dosing days of each phase. The groups allocations were reversed in Phase II. Blood sampling was performed as outlined in Phase I.

All animals met the selection criteria and were clinically examined prior to and during the course of the study. General health observations were carried out throughout the study and animals remained in good health.

During the entire in-life study, mortality checks and clinical observations were performed on each animal twice daily. They were also performed immediately after dosing and then at regular intervals throughout the day of treatment (during blood collections).

No mortality occurred during the study. Emesis (slight, foamy and/or brown vomiting) and liquid feces (moderate to severe) were observed occasionally in 4/24 animals from both of the dosed groups.

There were no significant variations in body weight or food consumption observed during this study. Each blood sample was collected by vein puncture directly into a labeled 2.6ml heparin tube.

Samples were stored on crushed ice after collection and plasma was separated by centrifugation (10 min at 3000rpm) within two hours of sampling. The analysis of Meloxicam was performed at Analyst Research Laboratories Hamada St. 12, Rehovot 76703, Israel using a fully validated method (Part II Q).

Bioequivalence is demonstrated if "*under the identical and appropriate experimental conditions, the bioavailability of the active substance only differs within acceptable limits.*" And bioavailability is defined by" *the rate and extent to which the active substance reaches the systemic circulation and becomes available to the site(s) of action.*" The standard equivalence limits are 80% - 125% (implying a 5% level of significance).

Summary of the pharmacokinetic parameters which were calculated for the bioequivalence evaluation are the area under the plasma concentration versus time curve (AUC), the maximum concentration (C_{max}), the time to maximum concentration (Tmax) and the half-life ($t_{1/2}$) are presented in tables 11 and 12.

Table 11 (a and b): Pharmacokinetic parameters derived following oral administration of test compound, Meloxicam 2.5 mg tablet administered to dogs,(Dog study No 101-106 & 151-156) at a dose level of 0.2 mg/kg bw.

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Treatment	Meloxicam 2.5 mg/Tablets (Test compound)					
Parameter	Males					
Dog Number	101	102	103	104	105	106
$t_{1/2}$ (hr)	29.1	32.3	23.1	29.3	21.9	26.8
Tmax (hr)	24.0	5.0	24.0	24.0	8.0	24.0
Cmax (ng/ml)	523.0	524.0	487.7	502.7	490.0	716.0
AUC_{INF} ng*hr/ml	28288.3	29467.8	20330.2	28347.3	18691.3	35461.1

Treatment	Meloxicam 2.5 mg/Tablets (Test compound)					
Parameter	Females					
Dog Number	151	152	153	154	155	156
$t_{1/2}$ (hr)	23.8	19.9	25.0	24.0	22.2	22.0
Tmax (hr)	6.0	24.0	3.0	3.0	24.0	3.0
Cmax (ng/ml)	551.6	688.1	673.9	550.6	541.4	571.4
AUC_{INF} ng*hr/ml	25379.7	29106.2	28750.2	24829.4	25883.6	25234.7

Table 11 (c and d) (continued): Pharmacokinetic parameters derived following oral administration of test compound, Meloxicam 2.5 tablet administered to dogs (Dog study No 201-206 & 251-256), at a dose level of 0.2 mg/kg bw.

Treatment	Meloxicam 2.5 mg/Tablets (Test compound)					
Parameter	Males					
Dog Number	201	202	203	204	205	206
$t_{1/2}$ (hr)	22.8	25.5	25.3	20.4	21.8	26.5
Tmax (hr)	10.0	24.0	9.0	12.0	9.0	24.0
Cmax (ng/ml)	469.4	458.6	622.4	531.0	463.6	565.0
AUC_{INF} ng*hr/ml	20532.1	23969.2	30647.2	21284.2	19898.5	30731.6

Treatment	Meloxicam 2.5 mg/Tablets (Test compound)					
Parameter	Males					
Dog Number	251	252	253	254	255	256
$t_{1/2}$ (hr)	28.6	20.4	26.0	26.1	23.0	23.1
Tmax (hr)	1.0	24.0	8.5	3.0	24.0	1.0
Cmax (ng/ml)	726.6	782.7	684.2	525.3	588.9	443.1
AUC_{INF} ng*hr/ml	30563.3	31089.4	33134.3	14978.0	28206.6	21504.9

Table 12 (a and b): Pharmacokinetic parameters derived following oral administration of reference compound, Metacam 2.5 tablet administered to dogs (Dog study No 101-106 & 151-156), at a dose level of 0.2 mg/kg bw.

Treatment	Metacam® 2.5 mg/Tablets (Reference compound)					
Parameter	Males					
Dog Number	101	102	103	104	105	106
$t_{1/2}$ (hr)	27.8	29.8	25.8	30.2	20.6	27.2
Tmax (hr)	24.0	24.0	24.0	24.0	5.0	24.0
Cmax (ng/ml)	557.4	612.7	397.6	533.0	539.1	591.3
AUC_{INF} ng*hr/ml	29762.1	34460.2	20760.8	30734.1	23236.2	33383.1

Treatment	Metacam® 2.5 mg/Tablets (Reference compound)					
Parameter	Females					
Dog Number	151	152	153	154	155	156
$t_{1/2}$ (hr)	21.3	20.3	25.0	24.5	22.6	21.7
Tmax (hr)	5.0	9.0	3.0	5.0	5.0	3.0
Cmax (ng/ml)	1108.6	604.9	634.7	616.8	663.6	546.6
AUC_{INF} ng*hr/ml	27743.1	28309.8	33136.6	26689.2	31059.8	23854.5

Table 12 (c and d) (continued): Pharmacokinetic parameters derived following oral administration of reference compound, Metacam® 2.5 tablet administered to dogs(Dog study No 201-206 & 251-256), at a dose level of 0.2 mg/kg bw.

Treatment	Metacam® 2.5 mg/Tablets (Reference compound)					
Parameter	Males					
Dog Number	201	202	203	204	205	206
t1/2 (hr)	25.7	21.3	28.6	20.4	23.1	29.6
Tmax (hr)	10.0	5.0	10.0	8.0	3.0	24.0
Cmax (ng/ml)	513.7	657.3	479.0	590.2	480.7	593.2
AUC_{INF} ng*hr/ml	2416 9.3	2310 5.4	2664 3.4	2234 5.1	1983 8.8	30851.2

Treatment	Metacam® 2.5 mg/Tablets (Reference compound)					
Parameter	Females					
Dog Number	251	252	253	254	255	256
t1/2 (hr)	24.7	20.9	28.2	25.6	22.9	27.2
Tmax (hr)	24.0	3.0	7.0	3.0	24.0	8.5
Cmax (ng/ml)	687.5	618.3	570.8	442.2	635.1	411.5
AUC_{INF} ng*hr/ml	3943 4.8	2898 6.8	3016 7.1	1427 4.7	3353 5.3	24650.5

The statistical analysis evaluation for the bioequivalence CV calculation is presented in Table 13 below

Table 13: Statistical analysis evaluation for the bioequivalence CV calculation

Parameter	MSE	DF	Mean reference	Mean test	Mean ref – Mean test
ln AUC	0.00612	21	10.2018996	10.14955	0.0523467
ln Cmax	0.023355	21	6.35363658	6.332934	0.0207022
ln T1/2elm	0.003802	21	3.20214335	3.192854	0.0092892

Table 13 (continued): Statistical analysis evaluation for the bioequivalence CV calculation

Parameter	Back transformed				
	Lower 90% CL	Upper 90% CL	Ratio of geometric means	Lower 90% CL	Upper 90% CL
ln AUC	0.01348	0.09121	1.053741	1.01357	1.0955
ln Cmax	-0.0552	0.09663	1.020918	0.94628	1.10145
ln T1/2elm	-0.0213	0.03992	1.009332	0.97888	1.04073

The ANOVA statistical analyses results sourced from the variance estimates and the confidence limits for AUC, Cmax and $t_{1/2}$ present that all the confidence limits are within the 0.8 -1.2 range.

Conclusion of bioequivalence study

Bioequivalence of the test and reference items was confirmed, where the 90% confidence interval for AUC and Cmax for meloxicam is within the limits of 80% – 125%. The ANOVA statistical analyses results sourced from the variance estimates and the confidence limits for AUC, Cmax and $t_{1/2}$ demonstrate that all the confidence limits are well within the 0.8 -1.2 range.

Based on the results of the in-life animal phase, the results of the meloxicam plasma

analytical phase, the resulting derived pharmacokinetic parameters and their subsequent bioequivalence statistical analysis, it is concluded that Meloxicam 2.5 mg tablet for dogs manufactured in accordance with Example 1 is bioequivalent to the registered Reference Compound Metacam® tablet for dogs (Manufacturer Boehringer Ingelheim Vetmedica)

Thus, the results of the bioequivalence study show that the products are bioequivalent within 90% confidence limits and within the 80 - 125% established in the Guideline EMEA/CVMP/016/00 *Guidelines for the conduct of the bioequivalence study for veterinary medicinal products*. On this basis, Meloxicam Tablet 2.5 mg is considered to be essentially similar to Metacam Tablet 2.5 mg.

Example 5

The following revised method may be used instead of the method of Example 1. The equipment and ingredients outlined in Example 1 were used in this example. It will also be understood that this method produces identical meloxicam tablets to that of Example 1. Both methods are suitable for scaling up to an industrial scale, however, this method facilitates easier scaling up by slightly altering the mixing of the ingredients in the pre-lubrication step. The method of this example is outlined in Figure 2.

The method below relates to the manufacture of 1mg and 2.5mg tablets, however, other tablets may be contemplated and the weight of ingredients will be altered accordingly.

Pre-Lubrication Blending and Lubrication:

1. Meloxicam, approximately 0.4kg, was mixed with an approximately equal amount of Lactose.

2. Approximately double the amount of lactose from step 1 was added to the mixture of step 1 and mixed. This mixture was sieved through a 40# mesh sieve.

3. Approximately double the amount of lactose from step 2 was added to the sifted mixture and mixed further for approximately 1 to 10 minutes, preferably 1 to 5 minutes.

4. Approximately double the amount of lactose from step 3 was added to the sifted mixture and mixed further for approximately 1 to 10 minutes, preferably 1 to 5 minutes.

5. The mixture from step 4, together with Prosolv SMCC 50, Sodium acid citrate, Crospovidone and remaining quantity of lactose DCL15 was added into a drum mixer.

6. The pork flavour was sifted with talc and one scoop of approximately 1.5kg to 2kg of mixture from step 5 and mixed further to form a flavour mixture.

7. The flavour mixture was added to the drum mixer and mixed for approximately 20 minutes at a drum speed of approximately 32 rpm +/- 2rpm.

8. The magnesium stearate was sieved through a 20# mesh sieve and added to approximately 1Kg of the mixture from step 7.

9. The mixture from step 8 was added to the drum mixer and mixed further. Ideally, such blending is carried out to achieve uniformity of the active ingredient in the blend. This is generally when the homogeneity of the blend is 90 to 110% of the expected active content with a relative standard deviation (RSD) of 5% or less.

Compression:

10. The compression machined was tooled up.

11. The blend from step 9 was loaded into the compression machine programmed according to the desired tablet specification.

12. During the compression step, in-process analysis on the tablets was carried out to ensure the unit dose tablets were obtained with the desired properties.

CLAIMS:

1. A process for the manufacture of an orally administrable palatable unit dose tablet comprising

meloxicam from 0.1% to 5% by weight wherein meloxicam has a particle size wherein at least 90% by weight of the meloxicam particles are less than 10 microns in diameter;

a first and second filler from 70% to 95% by weight wherein the first filler has a particle size wherein 100% by weight of the particles are less than 500 microns in diameter, at least 90% by weight of the particles are less than 355 microns in diameter, between 40 to 70% by weight of the particles are less than 150 microns in diameter, and a maximum of 30% of the particles are smaller than 75 microns in diameter; and the second filler has an average particle size of approx. 60 μm;

one or more disintegrating agents from 1% to 5% by weight wherein the disintegrating agent has an average particle size of approximately 100 microns to 130 microns in diameter;

one or more flavouring agents from 1% to 10% by weight;

one or more stabilizing agents from 1% to 10% by weight wherein the stabilizing agent has an average particle size of approximately 150 microns to 700 microns in diameter;

one or more lubricants from 0.1% to 5% by weight wherein the lubricant has an average particle size of approximately 35 microns to 100 microns in diameter; and

one or more glidants from 0.1% to 5% by weight wherein the glidant has an average particle size of approximately 10 microns to 150 microns in diameter;

wherein the process comprises the following steps

i) a pre-lubrication blending step comprising

mixing the meloxicam with an approximately equal amount of a first filler, adding further first filler and sieving through a 40# mesh sieve to form a sifted mixture, adding further first filler to the sifted mixture and mixing further to form a meloxicam/first filler mixture;

mixing the remaining first filler, second filler, disintegrating agent and stabiliser with the meloxicam/first filler mixture and placing the resultant mixture in a drum;

mixing the flavouring agent with the glidant to form a flavouring mixture and adding the flavouring mixture to the drum; and

mixing all the ingredients to form pre-lubrication granules;

ii) a lubrication step comprising adding the lubricant to the pre-lubricated granules and mixing to form a lubricated mixture; and

iii) a direct compression step to form an orally administrable palatable unit dose tablet with a friability of less than 1% after 4 minutes and a disintegration time of less than 15 minutes.

2. The process as claimed in claim 1 wherein the direct compression step comprises

feeding the lubricated mixture into double polythene lined drums and transferring the lubricated mixture into a hopper;

feeding the lubricated mixture from the hopper into a die cavity of a compression table press;

forming unit dose tablets under direct compression to achieve unit dose tablets with friability of less than 1% after 4 minutes and a disintegration time of less than 15 minutes;

discharging the tablets from the table press into a chute; and

Packaging the tablets.

3. An orally administrable palatable unit dose tablet comprising

meloxicam from 0.1% to 5% by weight wherein meloxicam has a particle size wherein at least 90% by weight of the meloxicam particles are less than 10 microns in diameter;

a first and second filler from 70% to 95% by weight the first filler has a particle size wherein 100% by weight of the particles are less than 500 microns in diameter, at least 90% by weight of the particles are less than 355 microns in diameter, between 40 to 70% by weight of the particles are less than 150 microns in diameter, and a maximum of 30% of the particles are smaller than 75 microns in diameter and the second filler has an average particle size of approx. 60 μm;

one or more disintegrating agents from 1% to 5% by weight wherein the disintegrating agent has an average particle size of approximately 100 microns to 130 microns in diameter.

one or more flavouring agents from 1% to 10% by weight;

one or more stabilizing agents from 1% to 10% by weight wherein the stabilizing agent has an average particle size of approximately 150 microns to 700 microns in diameter;

one or more lubricants from 0.1% to 5% by weight wherein the lubricant has an average particle size of approximately 35 microns to 100 microns in diameter; and

one or more glidants from 0.1% to 5% by weight wherein the glidant has an average particle size of approximately 10 microns to 150 microns in diameter;

wherein the tablet has a friability of less than 1% after 4 minutes and a disintegration time of less than 15 minutes.

4. The orally administrable palatable unit does tablet according to claim 3 or manufactured in accordance with claim 1 or claim 2 wherein the first filler is lactose monohydrate, the second filler is silicified microcrystalline cellulose, the disintegrant is cross-linked N-vinyl-2-pyrrolidone, the lubricant is magnesium stearate, the glidant is talc, the stabiliser is sodium citrate and the flavouring agent is a pharmaceutically acceptable synthetic flavouring agent.

5. An orally administrable palatable unit dose tablet and process for manufacture thereof as hereinbefore described with reference to the accompanying Figures and Examples.

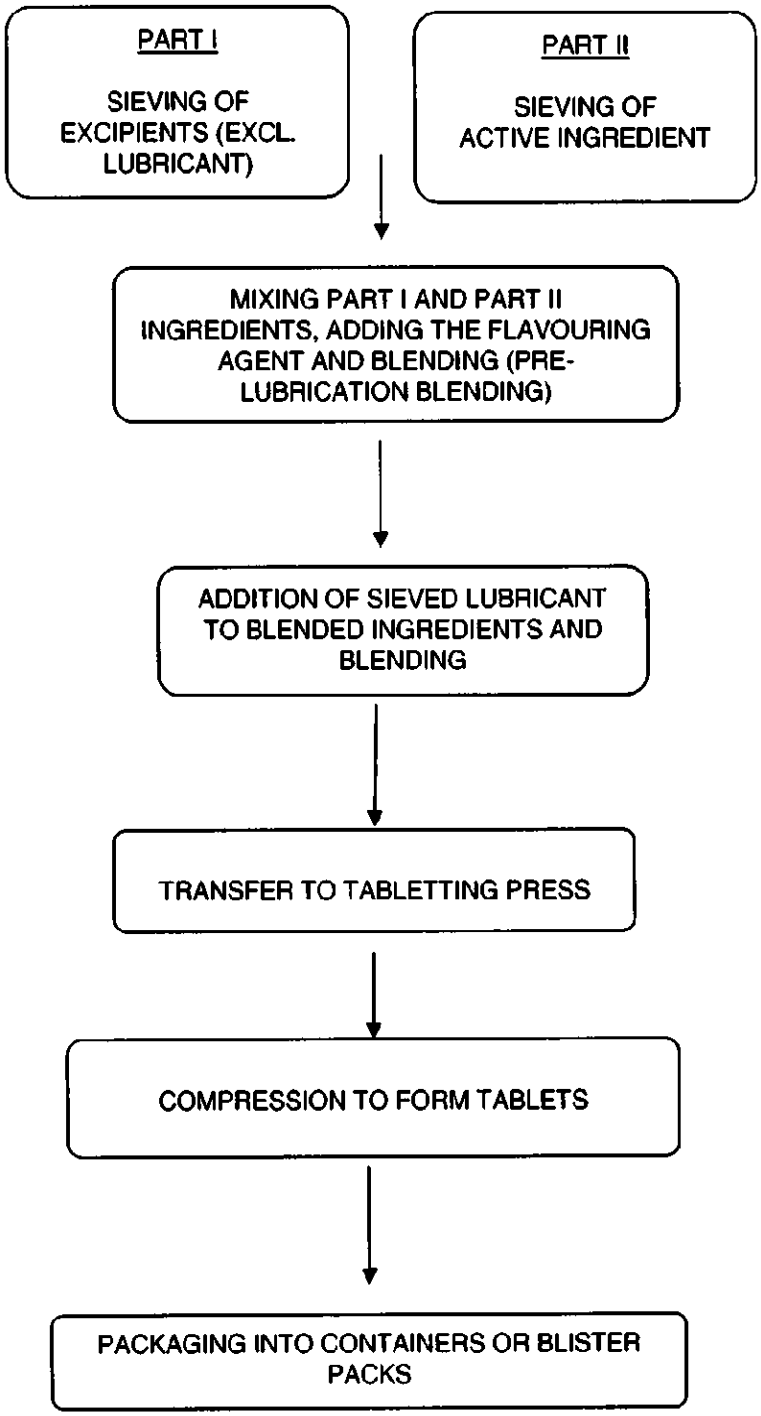
PART I
SIEVING OF EXCIPIENTS (EXCL. LUBRICANT)
PART II
SIEVING OF ACTIVE INGREDIENT
MIXING PART I AND PART II INGREDIENTS, ADDING THE FLAVOURING AGENT AND BLENDING (PRE-LUBRICATION BLENDING)
ADDITION OF SIEVED LUBRICANT TO BLENDED INGREDIENTS AND BLENDING
TRANSFER TO TABLETTING PRESS
COMPRESSION TO FORM TABLETS
PACKAGING INTO CONTAINERS OR BLISTER PACKS

Fig. 1

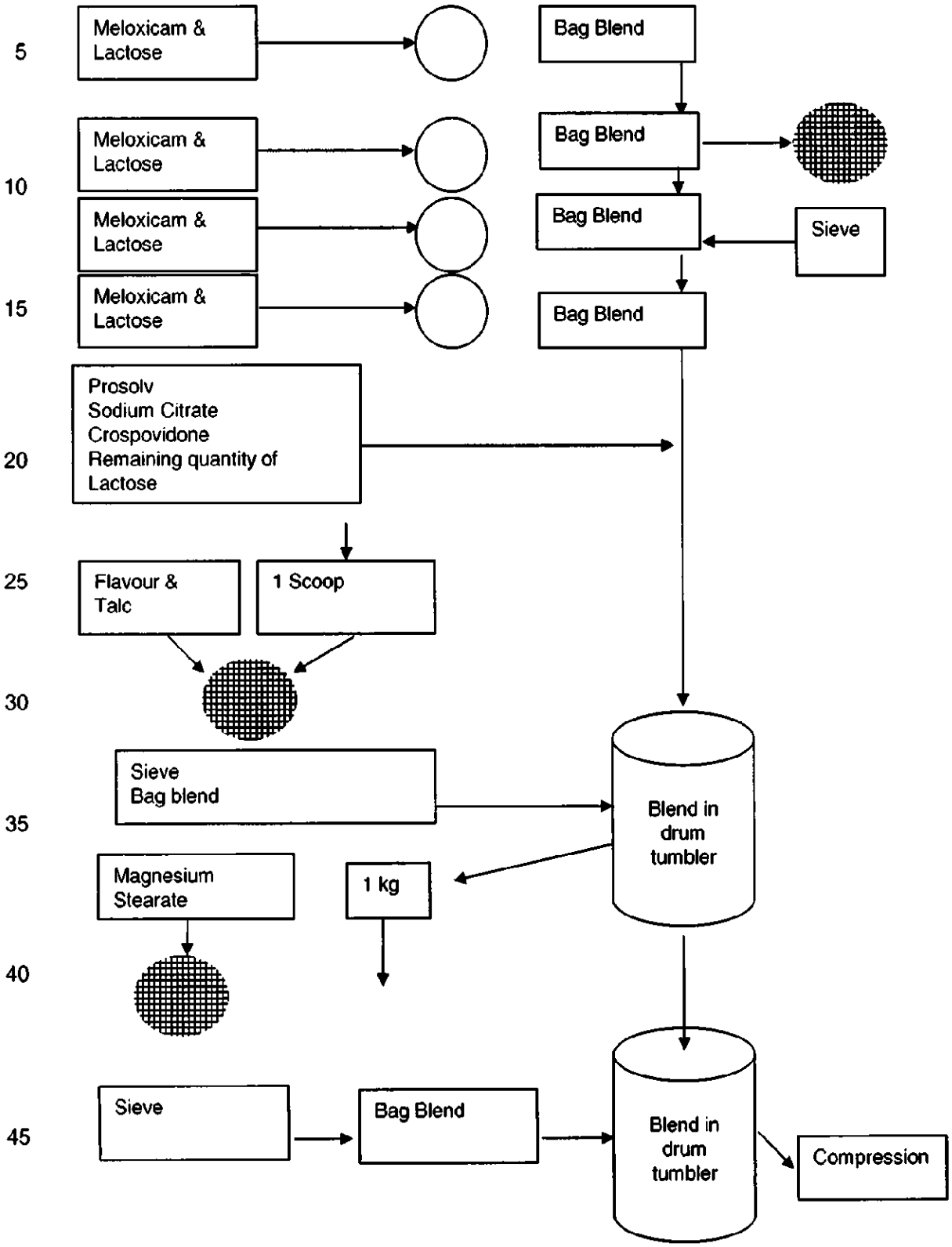
Meloxicam & Lactose
Meloxicam & Lactose
Meloxicam & Lactose
Meloxicam & Lactose
Bag Blend
Bag Blend
Bag Blend
Bag Blend
Sieve
Prosolv
Sodium Citrate
Crospovidone
Remaining quantity of Lactose
Flavour & Talc
1 Scoop
Sieve
Bag blend
Blend in drum tumbler
Magnesium Stearate
1 kg
Sieve
Bag Blend
Blend in drum tumbler
Compression

Fig. 2