DRUG DEVELOPMENT COMMUNICATIONS, 2(3), 259-276 (1976)

SOME RECENT ADVANCES IN THE PACKAGING OF PHARMACEUTICALS (II)

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Part I of this paper was published in Drug Development Communications, Vol. II, No. 2

IV PACKAGING TECHNOLOGY

The development of pharmaceutical formulations has to be closely linked with packaging technology as the successful marriage between product and pack requires sound knowledge of both. Therefore before the pack and the packaging operation can be considered certain basic information along the following lines must be considered.

i) Product deterioration with particular reference to the primary drug substance(s). - does it occur naturally or can it be restricted or prevented by exclusion of light, oxygen, carbon dioxide, temperature changes or by packaging under an inert atmosphere? Is it sensitive to pH changes or certain ingredients when in contact with any packaging materials i.e. can pack be a means of maximising product shelf life?

ii) Specific Formulation Aspects i.e. - possible loss of volatile constituents, retention of preservatives, possible compatibility, absorption, with packaging materials etc requirements for sterility, and maintenance of sterility, low particulate contamination etc.

iii) Product - will it suffer from mechanical damage or physical deterioration i.e. separation, breakage etc. either during handling or once in the pack.

iv) Product form - size - weight/volume variations.

v) Dosage and quantity - combined with iv to give pack quantity for treatment.

The product characteristics then have to be combined with aspects related to the delivery or administration of the dose which in turn may be closely associated with user convenience, medical-marketing factors which must assist in conveying confidence in the product by the pack presentation and the total cost factor of the pack. Thus with this background knowledge of the product, product(s) and pack(s) or packaging materials are then brought together in a series of feasibility tests. This stage is essential for both information and the economical aspects of testing, particularly as the third stage, formal stability tests with the final pack of choice becomes relatively costly in money and time if it is only used to establish that a certain pack-product relationship is unsatisfactory. In depth testing of the pack under a range of conditions commences at the feasibility stage. However before actual contact is made with the product certain basic information and checks must be carried out on the packaging materials i.e.

i) Write up a provisional specification for all packaging materials to be involved in tests. These should include a complete material breakdown if practical.

ii) Check that samples match the specification in terms of dimensions, construction, type of material - either analytically check that materials are as declared or request a warranty certificate of ware from supplier.

iii) Identify supplier, batch reference material and most important put aside reference samples as a safeguard against any changes occurring at any

future stage (whether authorised or otherwise) so that it can be identified by comparative testing.

iv) If plastic, carry out NF extractive tests including checks on toxicity and irritancy.

These initial stages are the basis for any product-pack stability as one of the most prevalent errors in the past was insufficient knowledge on what was being employed for testing. Hence an essential factor is to thoroughly 'know' what is being tested. When the product and pack are brought together at this feasibility stage it is advisable that all operations are recorded in terms of both good manufacturing practice and quality assurance e.g. such factors as volume filled, cap torques, filling conditions (temperature and RH), heat sealing temperature/dwell/ pressure etc should all form part of the test records. Although it is normal practice to challenge the product/pack system to accelerated conditions which is useful for determining reactions, migration, sorption etc between product and pack, product deterioration may occur due to the pack breaking down under conditions which it will never meet in actual practice. It is therefore important either to limit the testing to conditions which the pack will withstand or recognise that undue stresses will be applied if packs are stored at extremes of temperature and humidity for prolonged periods. Companies use various temperature ranges from around $-21^{o}C$ to as high as $80^{o}C$. In practice even exposure to 45^{o} - $50^{o}C$ for lengthy periods can cause pack deterioration; thus if these are acceptable as reasonable maxima the packs must be critically monitored for signs of deterioration. Refrigeration conditions ($4^{o}C$) generally provide the least change and can in most circumstances be considered a control

type condition. Product in sealed neutral glass ampoules can be used as a pack control, but even this has limitations due to the pack becoming a pressurised system at higher temperatures.

It must be stressed that apparently accelerated conditions which are normally associated by a range of temperature increases, can occasionally act the other way, particularly in the case of some packaging materials. The writer can recall a test on a Zinc and Castor oil Cream in an impact modified polystyrene jar fitted with a four start lug closuring system, which was selected for easing removal by the mother when holding the baby. This type of closure concentrates the applied stress to four relatively small areas - unlike a conventional continuous single start screw thread which has a greater thread to thread contact area. This can lead to a stress cracking situation. Jars stored at $4^{o}C$, $20^{o}C$, $30^{o}C$ and $37^{o}C$ cracked after 2 months, 6 months and 9 months respectively at the lower temperatures but not all at $37^{o}C$ thus indicating an acceleration affect as the temperatures decreased. It was therefore assumed that the phenomenon was mainly physical rather than a physico-chemical time/stress cracking effect i.e. the polymer was under the greatest stress at $4^{o}C$ whereas at increased temperatures the plastic tended to become more flexible and thereby the stress was relieved.

Extremes of humidity can also create problems. For example low RH and high RH can lead to delamination of paper based laminates. High RH, readily leads to a shower effect if a drop in temperature occurs. Laminations, metal containers and closures are placed under particularly severe conditions if a condition approaching $37^{o}C/95\%$ is employed. Metal shelves or metal fitments should not be used in testing areas of high humidity, as this not only leads to corrosion, but possible interaction with metal pack components e.g. bimetallic corrosion of aluminium foil.

Finally few world wide conditions (except in controlled circumstances have static temperature and RH conditions so there is a further choice of either a cycling cabinet (15°C/50% RH 12 hours 37°C/90% RH 12 hours is a popular choice), regularly transferring packs between different conditions or carrying out tests under actual field trial locations. However at the feasibility stage the choice has usually to be restricted to simulated laboratory conditions as a pack choice frequently has to be made in 3-6 months. Tests during this period should also cover exposure to light and what is extremely important, a simulated in use test, as products have been known to change during the in use period or even more likely, reveal deficiences in the pack. Once feasibility studies have enabled the final pack/product to be chosen, formal stability tests on three batches of product can be prepared. These require the same detail and documentation indicated earlier plus sufficient samples for initial analytical tests to statistically establish with confidence limits, the composition of the product and the pack. It is common practice to store product/packs under a range of conditions i.e. 4°C, 15°C, 25°C, 30°C, 37°C/30% RH, 37°/75% RH 45°C etc but only selectively carry out analysis on certain conditions (e.g. 4°C, 30°C, 37°C, 75% RH). The other conditions are used as reserves which can be checked if changes are found to occur at the main conditions and supplementary data is required. The 45°C condition would normally only be analysed up to 12 months as the likelihood of pack deterioration is considerable under such a continuously high condition. Analysis intervals most used are 0, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months. Although many regulatory authorities permit some degree of shelf life prediction in the early stages of testing e.g. 2 years shelf life based on 6-12 months good data at 37°C to 45°C, further life extension may have to be proved by storage at identified temperatures over the full period. There is also a suggestion

that unfilled packs should be stored alongside the filled product-packs so that any changes in the pack can be more closely monitored. With attempts to standardise storage recommendations on labels and cartons it is important that temperatures used for storage tests bear close resemblance to these conditions. It is also important that all storage points are checked and recorded on a daily basis and that if cabinets or rooms fail, these are covered by a 'fail safe' procedure. This may either consist of an alarm system coupled to company security or the automatic shut down of heat or steam should these give rise to temperature or RH increases in a failure situation. The failure of storage areas at a two year stability stage may prevent shelf life extension, prove costly on recall due to short expiry dates and in terms of repeat stability tests.

Formal stability tests are becoming increasingly more expensive in terms of analytical, microbiological and toxicological testing. Programmes must be effectively drawn up prior to initiating any test. Although computerisation can considerably assist, thorough investigation into the accuracy, sensitivity and reproducability of analytical methods is essential before a formal stability programme is commenced. This applies to both packaging and product.

It can therefore be concluded that packaging technology has to maintain close coordination with product formulation and those responsible for any stability programmes, irrespective of whether a feasibility or formal type test in involved. At every stage when a packed product is removed from test it is important that pack examination is carried out both before and after the product is extracted for analysis.

It is only by adopting such procedures that full confidence in the marriage of a product and pack can be successfully established to the satisfaction of all concerned. Good team work is essential.

V CONCLUSION

The packaging of pharmaceuticals remains relatively conservative, and therefore many of the modern trends seen in the packaging of other items are only adopted once they become well established elsewhere. Specialised packaging, which is restricted to the pharmaceutical industry is not only slow to develop but tends to be associated either with new or improved modes of administration or such trends as the unit dose form. The title of this paper has been deliberately restricted to very broad issues from which can grow a fuller knowledge of relationships between product and pack. Virtually any of the general examples given can be expanded to a topic in itself. Although a liberal set of references are included the author has so far mainly drawn on his own experience, which results from some thirty years serving various aspects of the pharmaceutical industry. The subject of child resistant packaging has been deliberately excluded as so much has been said on this emotional subject in the past few years that it appears wise to let the dust settle until a full picture emerges.

The relationship of packaging to the conservation of the world's natural resources including energy supplies will have to be taken into account in the future. Factors such as pollution disposal, recycling and reuse will have to be considered as part of the total packaging concept. However this again is better dealt with as a separate subject.

Finally packaging can only be effective if the total system, of which it is part, is properly specified and monitored. This means that the product, pack and the means by which the product is manufactured

and packed must all be adequately specified and subject to good manufacturing practice and quality assurance. No change to either the materials or the process must be made without full assessment to confirm that the product stability profile has not been altered. Although the ultimate success of a product is primarily related to its efficacy, packaging provides an essential role in terms of confidence which is related to presentation, protection, identification and convenience. Any user complaints which arise are a final means of assessing product pack success provided they are judged in the light of overall sales.

I am particularly indebted to Mr. P.L. Corby for his assistance in producing this paper.

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