Concept of fast dissolving formulations for use in acute treatment conditions – introspection, thoughts and perspectives

Sir,

In a recent issue of AJP, Ranagasamy *et al.* (2009) have provided a succulent report on the development of a fast dissolving tablet of terbutaline sulfate for possible human use in the timely management of asthmatic episodes.[1] The design and evaluation part of the work suggested that careful consideration was taken from the selection of excipients until the dissolution testing of the tablets to confirm its intended utility.[1] However, an important missing link in this work was to confirm whether or not such a system would work under *in vivo* conditions to ensure rapid drug delivery has not been compromised. Hence, it need to be questioned and challenged when emphatic conclusion stating that "the new fast dissolving terbutaline formulation is better than the conventional tablet dosage form used in the management of asthma" has been made in the published work without adequate support to back it up.[1] While it is acknowledged that it may be difficult for academic/research institutions or fledgling biotechs to perform *in vivo* evaluations due to the lack of resources, trained personnel and/or funding issues, in some extraordinary cases it may be a good idea to explore testing of the new formulation in a preclinical model for getting clarity on the *in vivo* performance of the new formulation. Needless to say, the final utility of the innovation and design of the new formulation is solely dependent on its *in vivo* performance.

This communication is intended to draw the attention of researchers who put incredible efforts and exercise diligence in the research work of fast dissolving formulation development scenarios. As the name suggests, the formulations that are classified in this category need to be delivering the drug very rapidly and more efficiently than a regular formulation. While the design, development and evaluation using *in vitro* systems is an important component to ensure a "desired *in vitro* profile" is attained, it is equally important that such new formulation prototypes be put in an *in vivo* study either in a preclinical model or in human subjects. In the testing of the formulation attributes in the *in vivo* studies by using pharmacokinetic surrogates, it is imperative to compare the "new formulation" with the existing/conventional formulation with a well-defined null hypothesis and adequate sample size to conclude whether or not "null hypothesis" is valid by proper statistical evaluation of the pharmacokinetic data generated in the study.

The following considerations could be instituted to better utilize the *in vitro* data gathered in such investigations.

Firstly, the area of applicability for fast dissolving formulations is where the pharmacodynamic response needs to be obtained very quickly as in acute conditions such as dental pain, migraine attacks, etc. However, there may be situations where preference to fast dissolving formulations may be considered in therapies related to children and/or in geriatric population since they may have difficulty in swallowing regular tablets with required fluid intake and/or provide added convenience.[2,3] It is imperative to understand and appreciate the physiological influence the acute disease may carry–possible alteration of the gastrointestinal conditions to negate the purported beneficial effects derived from the new formulation. For example, it was shown that a newly developed fast dissolving tablet of meloxicam was much superior to the regular tablet in vagally suppressed rats.[4] However, in control rats (not subjected to vagal suppression) the performance of the fast dissolving formulation was comparable to the regular tablet. Hence, this study showed that during vagal suppression (likely to happen during pain episodes), fast dissolving tablets are a better choice as the bioavailability of the drug delivered in that formulation remains unaltered as opposed to regular tablets whose bioavailability may be severely compromised during vagal suppression.[4] The human relevance of acute dental pain slowing the absorption rate of regular ibuprofen tablets and the paramount importance of fast dissolving ibuprofen tablets was confirmed by the same workers.[5] Therefore, the availability of fast dissolving ibuprofen tablets was able to overcome the physiological challenge imposed by the acute dental pain in human subjects.[5]

Secondly, it may be very important to perform literature search and seek if an IVIVC (*in vitro in vivo* correlation) has been already established for the compound that is being formulated.[6,7] The availability of a confirmed "IVIVC" correlation would enable the researcher to draw a reasonable projection of the *in vitro* data to a quantifiable *in vivo* outcome (such as a faster rate of

release relating to both rapid and higher achievement of peak concentration the drug). Since it is always a fair question to ask as to what *in vitro* data would translate under *in vivo* setting, such a home-work may bridge the understanding without ambiguity. The availability of a failed "IVIVC" correlation would make it much harder for the researcher to comprehend the outcome of the *in vitro* data even though diligent efforts were put in the design and release of the new formulation. If no 'IVIVC' correlation has been reported for the compound (and/or the class in general), it would make it tricky for the interpretation of the *in vitro* data to an *in vivo* situation.

Thirdly, regardless of the availability or the lack of availability of IVIVC data package, it may be extremely beneficial to correlate peak concentration and exposure data already published in the literature to the type of formulation (solution, suspension, immediate release tablet or slow release formulation) which was tested in that study. For instance, if an immediate release formulation was used, the attainment of *in vivo* peak plasma concentration at 0.5 h may suggest the propensity for the drug to get absorbed from stomach and/or upper gastrointestinal tract itself. This would provide a basis as to how rapid the dissolution of the new formulation needs to be in order to perform better as compared to the already existing formulation.

Fourthly, if practically feasible, it would make perfect scientific sense to try out the dissolution profile of existing marketed formulation(s) for the compound in question under the same conditions being used for the new formulation. Such a comparison, if done in an unbiased manner, would enable researcher to better understand and appreciate the likely contributions that the formulations may produce in an *in vivo* study. For instance, if clear superiority in dissolution is observed for the new formulation, it may be reasonable to hypothesize that the *in vivo* peak concentration attainment could be faster with the new formulation. In this context, Aghazadeh-Habashi and Jamali (2008) showed that the newly dissolved fast dissolving tablet of meloxicam was completely disintegrated in mere 5 s and 30% dissolution was attained within 15 min and continued to be about 60% in 2 hours as compared to the regular tablet of meloxicam which took 5 min for complete disintegration and only 5.6% was dissolved in the first 30 min and the dissolution attained a plateau for the remaining 2 h time.[4] Likewise, Rangasamy *et al*.[1] have also shown that the new fast dissolving tablet of terbutaline was completely dissolved in 10 min as compared to a 50% dissolution observed from the convention tablet of terbutaline in 10 min.

Fifthly, there is a myth that fast dissolving formulations would always work under *in vivo* setting since it is difficult to comprehend that if a formulation dissolves very rapidly *in vitro* it cannot fail under *in vivo* testing. Recently a well-characterized griseofulvin fast dissolving tablet that showed superior *in vitro* dissolution profile as compared to the tablets that used regular griseofulvin particles failed to achieve enhanced and/or rapid absorption *in vivo*.[8] The *in vivo* bioavailability/bioequivalence carried out in human subjects suggested comparable bioavailability between the new/improved formulation (i.e. fast dissolving) and the regular formulation of griseofulvin.[8]

In conclusion, in spite of establishing a well-designed fast dissolving tablet prototype with detailed *in vitro* characterization, the utility of such a formulation is dependent on its *in vivo* performance. It appears prudent to investigate at least in an indirect fashion the utility of the newly developed fast dissolving formulation by the various scenarios detailed in this communication, if an *in vivo* testing option is not possible.

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