

CHAPTER 2

REVIEW OF LITERATURE

2.1 REVIEW OF ORODISPERSIBLE TABLETS

Witold Brniak et al., 2015a revealed that orodispersible tablets (ODTs) have been successfully used in therapy for more than 20 years, there is still no compendial method of their disintegration time evaluation other than the pharmacopoeial disintegration test conducted in 800–900 mL of distilled water. Therefore, several alternative tests more relevant to *in vivo* conditions were described by different researchers. The aim of this study was to compare these methods and correlate them with *in vivo* results. Six series of ODTs were prepared by direct compression. Their mechanical properties and disintegration times were measured with pharmacopoeial and alternative methods and compared with the *in vivo* results. The highest correlation with oral disintegration time was found in the case of own-construction apparatus with additional weight and the employment of the method proposed by Narazaki et al. The correlation coefficients were 0.9994 ($p < 0.001$), and 0.9907 ($p < 0.001$) respectively. The pharmacopoeial method correlated with the *in vivo* data much worse ($r = 0.8925$, $p < 0.05$). These results have shown that development of novel bio-relevant methods of ODT's disintegration time determination is eligible and scientifically justified. **Witold Brniak et al., 2015b** reported that the Orodispersible tablets (ODTs) and orodispersible films (ODFs) are solid oral dosage forms disintegrating or dissolving rapidly when placed in the mouth. One of the main issues related to their preparation is an efficient taste masking of a bitter drug substance. Therefore, the aim of this study was to prepare and evaluate the micro particles intended to mask a bitter taste of the prednisolone and use them in further preparation of two orodispersible dosage forms. Micro particles based on the Eudragit E PO or

E 100 as a taste-masking agent were prepared with spray-drying technique. Tablets containing micro particles, co-processed ODT excipient Pharmaburst, and lubricant were directly compressed with single-punch tablet press. Orodispersible films were prepared by casting polymeric solutions of hydroxypropyl methylcellulose containing uniformly dispersed micro particles. Physicochemical properties of micro particles were evaluated, as well as mechanical properties analysis, disintegration time measurements and dissolution tests were performed for prepared dosage forms. Both formulations showed good mechanical resistance while maintaining excellent disintegration properties. The dissolution studies showed good masking properties of micro particles with Eudragit E 100. The amount of prednisolone released during the first minute in phosphate buffer 6.8 was around 0.1%. After incorporation into the orodispersible forms, the amount of released prednisolone increased significantly. It was probably the effect of faster micro particles wetting in orodispersible forms and their partial destruction by compression force during tableting process.

Carolina Visser J *et al.*, 2015a revealed that the quality by design (QbD) approach was applied for optimizing the formulation of extemporaneously prepared orodispersible films (ODFs) using Design-Expert Software. The starting formulation was based on earlier experiments and contained the film forming agents hypromellose and carbomer 974P and the plasticizer glycerol (Visser *et al.*, 2015). Trometamol and disodium EDTA were added to stabilize the solution. To optimize this formulation a quality target product profile was established in which critical quality attributes (CQAs) such as mechanical properties and disintegration time were defined and quantified. As critical process parameters (CPP) that were evaluated for their effect on the CQAs the percentage of hypromellose and the percentage of glycerol as well as the drying time were chosen. Response surface methodology (RMS) was used to

evaluate the effects of the CPPs on the CQAs of the final product. The main factor affecting tensile strength and Young's modulus was the percentage of glycerol. Elongation at break was mainly influenced by the drying temperature. Disintegration time was found to be sensitive to the percentage of hypromellose. From the results a design space could be created. As long as the formulation and process variables remain within this design space, a product is obtained with desired characteristics and that meets all set quality requirements.

Carolina Visser J et al., 2015b reported that the Orodispersible films (ODFs) are promising drug delivery systems for customized small scale pharmacy preparations. The aim of the present study was to develop a versatile casting solution suitable for the extemporaneous production of ODFs to which active pharmaceutical ingredients (APIs) can be added. Different combinations of film forming agents and other excipients and different casting heights were tested for their suitability for production of ODFs. The best suitable casting solution contained hypromellose, carbomer, glycerol, disodium EDTA and trometamol. This casting solution was used to prepare ODFs containing water-soluble APIs (enalapril maleate and prednisolone disodium phosphate) and a poorly water-soluble API (diazepam) for which ethanol 96% was used as co-solvent. The water soluble APIs as well as ethanol influenced the viscosity of the casting solution, mechanical properties and disintegration time of the ODFs. All ODFs containing API met the requirements on uniformity of mass and uniformity of content set by the European Pharmacopoeia (2014) (Ph. Eur.) 8th edition. In conclusion, ODFs of good pharmaceutical quality can be prepared on small scale. Hereby opening the perspective of using ODFs for individualized pharmacotherapy.

Maren Preis et al., 2014 revealed that there are no test procedures, definitions and specifications available how to determine mechanical strength of orodispersible

or buccal films. Aim of the study was to develop an appropriate and discriminating method to feature the evaluation of marketed and newly developed film products covering well-known and new approaches. The limits for mechanical strength were set starting from a puncture strength of 0.06 N/mm^2 according to the obtained results from marketed products. Furthermore, elongation to break of the marketed films (1.03–6.54%) and prepared film samples (4.51–33.17%) offered information on the film properties. The developed mechanical strength test method was suitable for all film types without the need of a pre-defined specimen. A mechanical strength threshold could be specified for future orodispersible film development.

Péter Szabó et al., 2014 revealed that the preformulation study of rotary spun hydroxypropyl cellulose fibers was carried out using the combination of textural characterization of gels in the concentration range of 42–60% w/w and optical microscopic evaluation of formed fibers. High adhesiveness values resulted in bead formation at lower polymer concentration, meanwhile fiber formation was hindered when high adhesiveness values were associated with high polymer content. The optimum gel concentration for fiber formation was given to 50% w/w. Drug loaded microfibers were prepared using a model drug of biopharmaceutical drug classification system class II. Fibers were milled, sieved and mixed with tableting excipients in order to directly compress orodispersible tablets. Hardness, friability, *in vitro* disintegration time values complied with the pharmacopoeial requirements. *In vitro* dissolution profiles obtained from three distinct dissolution media (pH 1.0; 4.5; 6.8) were quite differentiated compared to the compressed physical mixture of the same composition. Difference and similarity factors confirmed that the drug dissolution from microfiber based formula was almost independent from the pH value of the media. X-ray diffraction patterns indicated that the drug embedded in

microfibers was in amorphous state, and the decrease of o-Ps lifetime values suggested that fiber formation enabled the development of a more ordered fibrous system.

Harshal Pawar *et al.*, 2014 reported that the orodispersible tablets or fast dissolving tablets dissolve or disintegrate immediately on the patients' tongue or buccal mucosa. This drug delivery system is suitable for drugs undergoing high first pass metabolism. It improves bioavailability, reduces dosing, and thereby minimizes the side effects and also makes the dosage form more cost-effective. In this study, polysaccharide isolated from the seeds of *Cassia tora* was investigated as a superdisintegrant in the orodispersible tablets. The model drug chosen was valsartan, an antihypertensive drug. Valsartan tablets were prepared separately using different concentrations (1%, 2.5%, 5%, and 7.5% w/w) of isolated *C. tora* seed polysaccharide (natural) and sodium starch glycolate (synthetic) as superdisintegrant by the direct compression method. Evaluation of tablets was done for various pre- and post compression parameters. The stability studies were performed on optimized formulation F4. The disintegration time and *in vitro* drug release of the formulation F4 were compared with marketed formulations (conventional tablets). The drug excipient interactions were characterized by Fourier transform infrared studies. The formulation F4 containing 7.5% polysaccharide showed good wetting time and disintegration time as compared to a formulation prepared using a synthetic superdisintegrant at the same concentration level. Hence, batch F4 was considered optimized formulation. The present work revealed that *C. tora* seed polysaccharide has a good potential as a disintegrant in the formulation of orodispersible tablets. Because *C. tora* polysaccharide is inexpensive as compared to synthetic superdisintegrants, nontoxic,

compatible, and easy to manufacture, it can be used in place of currently marketed superdisintegrants.

Kadria A. Elkhodairy *et al.*, 2014 showed that the present study aimed to formulate orodispersible tablets of flutamide (FTM) to increase its bioavailability. Orodispersible tablets were prepared by direct compression technique using three different approaches namely; super-disintegration, effervescence and sublimation. Different combined approaches were proposed and evaluated to optimize tablet characteristics. Sodium starch glycolate(SSG) was used as the superdisintegrant. The prepared powder mixtures were subjected to both pre and post compression evaluation parameters including; IR spectroscopy, micromeritics properties, tablet hardness, friability, wetting time, disintegration time and *in vitro* drug release. IR studies indicated that there was no interaction between the drug and the excipients used except Ludipress. The results of micromeritics studies revealed that all formulations were of acceptable to good flow ability. Tablet hardness and friability indicated good mechanical strength. Wetting and dispersion times decreased from 46 to 38 s by increasing the SSG concentration from 3.33 to 6.66%w/w in tablets prepared by super disintegration method. The F8 formulation which was prepared by combined approaches of effervescence and superdisintegrant addition gave promising results for tablet disintegration and wetting times but failed to give faster dissolution rate. The incorporation of 1:5 solid dispersion of FTM: PEG6000 instead of the pure drug in the same formulation increased the drug release rate from 73.12 to 96.99% after 15 min. This increase in the dissolution rate may be due to the amorphization of the drug during the solid dispersion preparation. The presence of the amorphous form of the drug was shown in the IR spectra.

Bharat Damle *et al.*, 2014 showed that the Objective: The main goal of this study was to evaluate the bioequivalence of sildenafil ODT with and without water versus marketed sildenafil oral film-coated tablets. A secondary objective was to evaluate the effects of a high-fat meal on the pharmacokinetics of sildenafil ODT. The bioequivalence study of sildenafil ODT given with and without water versus marketed sildenafil citrate film-coated oral tablets was conducted in 36 subjects. In a food-effect study, the effect of a standard high-fat meal on the pharmacokinetics of sildenafil ODT was evaluated in 12 subjects. Both studies were randomized, open-label, crossover, single-dose (50 mg) studies in healthy men aged ≥ 18 years. Plasma samples were collected for 14 hours post dose, and pharmacokinetics were determined by using non compartmental analyses. All subjects in both studies were Asian males between the ages of 45 and 69 years. Sildenafil ODT without water was bioequivalent to the marketed sildenafil film-coated oral tablet as the 90% CI for the ratio of geometric means of C_{max} , $AUC_{0-\infty}$ and AUC_{0-last} were contained within equivalence limits (80%–125%). When sildenafil ODTs were given with water, the 90% CIs for sildenafil $AUC_{0-\infty}$ and AUC_{0-last} were contained within the range of 80% to 125%; however, the 90% CI for sildenafil C_{max} was not (79.76–92.78). This difference in C_{max} is unlikely to have any clinically meaningful impact. High-fat meals reduced the rate but not the extent of absorption of sildenafil. Mean C_{max} was reduced by 59%, and median T_{max} was delayed from 0.625 hour (fasting) to 4 hours (high-fat meal). However, AUC values were comparable between fed and fasted treatments. Sildenafil ODT, given with or without water, provides equivalent systemic exposure compared with marketed sildenafil film-coated oral tablets, thus offering a convenient alternative method of administration. Considering the results of the food-effect study, sildenafil ODT should be taken on an empty stomach.

Ritesh M Pabari, and Zebunnissa Ramtoola, 2012 reported that a two factor, three level (3^2) face centred, central composite design (CCD) was applied to investigate the main and interaction effects of tablet diameter and compression force (CF) on hardness, disintegration time (DT) and porosity of Mannitol based orodispersible tablets (ODTs). Tablet diameters of 10, 13 and 15 mm, and CF of 10, 15 and 20 kN were studied. Results of multiple linear regression analysis show that both the tablet diameter and CF influence tablet characteristics. A negative value of regression coefficient for tablet diameter showed an inverse relationship with hardness and DT. A positive regression coefficient for CF indicated an increase in hardness and DT with increasing CF as a result of the decrease in tablet porosity. Interestingly, at the larger tablet diameter of 15 mm, while hardness increased and porosity decreased with an increase in CF, the DT was resistant to change. The optimised combination was a tablet of 15 mm diameter compressed at 15kN showing a rapid DT of 37.7s value and of 71.4 N. Using these parameters, ODTs containing ibuprofen showed no significant change in DT (ANOVA; $p > 0.05$) irrespective of the hydrophobicity of the high of hardness ibuprofen.

Ahmed Abd Elbary *et al.*, 2012 revealed that the objective of this study was formulation, development and evaluation of meloxicam orodispersible tablets. ODTs were prepared by two methods including sublimation technique where different subliming agents like camphor, menthol and thymol were used with Ac-Di-Sol as a superdisintegrant. Each subliming agent was used in three different concentrations (5, 10 and 15% w/w). Tablets were first prepared and later exposed to vacuum. Meloxicam ODTs were also prepared by freeze-drying an aqueous dispersion of meloxicam containing a matrix former, a sugar alcohol, and a collapse protectant. In addition, different disintegration accelerators were tested (each in 1% w/v) including

PVP K25, PVP K90, PEG 6000, PEG 4000, PEG 400, tween 80 and tween 20. The prepared ODTs from two methods were evaluated for weight variation, thickness, drug content, friability, hardness, wetting time, in vitro disintegration time and in vitro dissolution study. The best formulation was subjected to stability testing for 3 months at temperatures 40 °C and 75% relative humidity and at 60 °C. All formulations showed disintegration time ranging from 1 to 46 s. All the prepared formulae complied with the pharmacopoeial requirements of the drug contents. T17 gave the best in vitro disintegration and dissolution results. ODT formula T17 has shown no appreciable changes with respect to physical characters, meloxicam content and dissolution profiles when stored at elevated temperatures. In conclusion the results of this work suggest that orodispersible tablets of meloxicam with rapid disintegration time, fast drug release and good hardness can be efficiently and successfully formulated by employing freeze drying and sublimation methods.

Dorrit Østergaard Nilausen *et al.*, 2011 reported that the aim of this study was to compare the bioavailability of orodispersible and conventional immediate-release (IR) escitalopram tablets. This was a randomized, open-label, 3-way crossover trial in which healthy men received single doses of orodispersible escitalopram formulations (2×10 mg and 1×20 mg) and conventional (2 ×10 mg) oral escitalopram tablets. Blood samples for pharmacokinetic analysis were obtained during a 168hour period after dosing. The safety profile and tolerability were assessed by monitoring of adverse events, physical examinations, ECGs, and clinical laboratory and vital signs assessments. A questionnaire was used to assess the perception of the orodispersible tablet (ODT). The assumed bioequivalence assessment was based on pharmacokinetic and statistical analysis of data from the 29 men who completed the 3 treatments. The serum concentration–time profiles of escitalopram were similar after intake of the 3

treatments. The 90% CI for the mean treatment ratios of the log-transformed C_{\max} , AUC_{0-t} , and AUC_{0-a} were all within the predefined equivalence range of 80% to 125%. Most subjects (87%) thought that the ODT was pleasant to take, and 85% of subjects thought that it was convenient to take the tablet without water. Most subjects (67%–90%) reported adverse events, with a similar incidence for all treatments. Most adverse events were mild, with somnolence and nausea being the most frequently reported. No clinically relevant changes were observed in physical, biochemical, hematologic, or urinalysis variables during the study. In this small study population of fasting healthy male volunteers, 2×10 -mg ODTs or 1×20 -mg ODT and 2×10 -mg conventional IR escitalopram tablets met the regulatory criteria for assumed bioequivalence.

Tae-Yong Shin *et al.*, 2010 revealed that the mast cell-mediated allergic symptoms are involved in many diseases, such as asthma and sinusitis. In this study, we investigated the effect of ethanol extract of fruits of *Prunus persica* (L) Batsch (FPP) on the mast cell-mediated allergic inflammation and studied the possible mechanism of action. FPP dose-dependently inhibited compound 48/80-induced systemic anaphylaxis and immunoglobulin E-mediated local allergic reactions. Histamine releasing from mast cells was reduced by FPP, which was mediated by modulation of intracellular calcium. In addition, FPP attenuated the phorbol 12-myristate 13-acetate and calcium ionophore A23187 (PMACI)-stimulated expression and secretion of pro-inflammatory cytokines in human mast cells. The inhibitory effect of FPP on pro-inflammatory cytokines was nuclear factor (NF)- κ B dependent. Our findings provide evidence that FPP inhibits mast cell-derived allergic inflammation and involvement of calcium and NF- κ B in these effects.

Puttewar TY *et al.*, 2010 showed that the Doxilamine orodispersible tablets were developed with considerable increase in drug release as compared to marketed formulations, seven formulations were developed and studied. The difference in drug release values was found to be 100.45 ± 1.89 and 56.47 ± 1.89 , respectively. To prevent bitter taste and unacceptable odour of the drug, the drug was taste masked with weak cation exchange resins like Indion 234, Indion 204 and Indion 414. The drug was characterized according to different compendial methods, on the basis of identification by UV spectroscopy, pH, organoleptic properties and other tests. Among the three resins, one was selected for further studies i.e., Indion 234, because of high drug loading capacity. Drug–resin complex was prepared using batch method and effect of various processing parameters viz. drug–resin ratio, pH, temperature and drug concentration was studied to optimize the loading conditions. Maximum loading was obtained at drug–resin ratio 1:2, pH 5, temperature 50°C and drug concentration 4 mg/ml. A successful taste masking of resinate was confirmed by time intensity method and also by taking drug release in 0.01 N hydrochloric acid and in simulated salivary fluid. The values of pre-compression parameters evaluated, were within prescribed limits and indicated good free flowing properties. The data obtained of post-compression parameters such as weight variation, hardness, friability, wetting time, water absorption ratio, content uniformity, disintegration time and dissolution and was found superior over conventional formulation. The F5 batch with disintegration time 25.24 ± 0.75 and dissolution $100.46\% \pm 3.78$ was selected as optimized formulation. This was compared with conventional marketed formulation and was found superior. Batch F5 was also subjected to stability studies for three months and was tested for its disintegration time, drug contents and dissolution behaviour monthly. It was observed that the contents of the tablets remained the same.

By an appropriate selection and combination of excipients it was possible to obtain orodispersible and taste masked tablets.

Sang-Hyun Kim et al., 2009 revealed that the mast cell-mediated immediate-type allergic reaction is involved in many allergic diseases such as asthma, allergic rhinitis, and sinusitis. Stimulation of mast cells starts the process of degranulation resulting in release of mediators such as histamine and an array of inflammatory cytokines. In this report, we investigated the effect of aqueous extract of *Teucrium japonicum* Houttuyn (Labiatae) (AXTJ) on the mast cell-mediated allergy model and studied its possible mechanisms of action. AXTJ inhibited compound 48/80-induced systemic reactions and serum histamine release in mice. AXTJ decreased immunoglobulin E-mediated passive cutaneous anaphylaxis reaction. AXTJ reduced histamine release and intracellular calcium from rat peritoneal mast cells activated by compound 48/80. In addition, AXTJ attenuated activation of nuclear factor (NF) κ B, and downstream tumour necrosis factor (TNF)- α expression in phorbol 12-myristate 13-acetate and calcium ionophore A23187-stimulated human mast cells. Our findings provide evidence that AXTJ inhibits mast cell-derived allergic reactions and involvement of intracellular calcium, TNF- α , and NF- κ B in these effects.

Jun Ho Lee et al., 2007 reported that the anti-allergic action of various Oriental medicinal herbs was investigated using in vitro and in vivo experimental models. Of these extracts, the ethanol extract of *Melaleuca* cortex (MC) exhibited the most potent activity in mast cells; its IC₅₀ values were 29 \pm 1.5 μ g/ml for antigen stimulation and 57 \pm 3.4 μ g/ml for thapsigargin stimulation. It inhibited compound-48/80-induced systemic anaphylaxis by 52.9% at a dose of 300 mg/kg in mice; it also inhibited the expression of the proinflammatory mediator TNF- α . With regard to its mechanism of action, MC suppressed the activating phosphorylation of Syk, a key enzyme in mast-

cell signaling processes and that of Akt in a dose-dependent manner. It also inhibited the MAP kinase ERK1/2, which is critical for the production of inflammatory cytokines in mast cells, as indicated by the suppression of the activating phosphorylation of ERK1/2. Taken together, these results suggest that the anti-allergic activity of MC may be due to the inhibition of histamine secretion and cytokine expression through the Syk inhibition in mast cells.

Giselle F. Passos *et al.*, 2007 showed that the anti-inflammatory and anti-allergic effects of the essential oil of *Cordia verbenacea* (Boraginaceae) and some of its active compounds were evaluated. Systemic treatment with the essential oil of *Cordia verbenacea* (300–600 mg/kg, p.o.) reduced carrageenan-induced rat paw oedema, myeloperoxidase activity and the mouse oedema elicited by carrageenan, bradykinin, substance P, histamine and platelet-activating factor. It also prevented carrageenan-evoked exudation and the neutrophil influx to the rat pleura and the neutrophil migration into carrageenan-stimulated mouse air pouches. Moreover, *Cordia verbenacea* oil inhibited the oedema caused by *Apis mellifera* venom or ovalbumin in sensitized rats and ovalbumin-evoked allergic pleurisy. The essential oil significantly decreased TNF α , without affecting IL-1 β production, in carrageenan-injected rat paws. Neither the PGE₂ formation after intrapleural injection of carrageenan nor the COX-1 or COX-2 activities *in vitro* were affected by the essential oil. Of high interest, the paw edema induced by carrageenan in mice was markedly inhibited by both sesquiterpenic compounds obtained from the essential oil: α -humulene and *trans*-caryophyllene (50 mg/kg, p.o.). Collectively, the present results showed marked anti-inflammatory effects for the essential oil of *Cordia verbenacea* and some active compounds, probably by interfering with TNF α production. *Cordia verbenacea*

essential oil or its constituents might represent new therapeutic options for the treatment of inflammatory diseases.

Tae-Yong Shin *et al.*, 2005 showed that the current study characterizes the mechanism by which the aqueous extract of *Lycopus lucidus* Turcz. (Labiatae) (LAE) decreases mast cell-mediated immediate-type allergic reaction. The immediate-type allergic reaction is involved in many allergic diseases such as asthma and allergic rhinitis. LAE has been used as a traditional medicine in Korea and is known to have an anti-inflammatory effect. However, its specific mechanism of action is still unknown. LAE was orally administered to mice for high and fast absorption. LAE inhibited compound 48/80-induced systemic reactions in mice. LAE decreased the local allergic reaction, passive cutaneous anaphylaxis, activated by antidinitrophenyl (DNP) IgE antibody. LAE dose-dependently reduced histamine release from rat peritoneal mast cells activated by compound 48/80 or anti-DNP IgE. Furthermore, LAE decreased the secretion of TNF- α and IL-6 in phorbol 12-myristate 13-acetate (PMA) plus calcium ionophore A23187-stimulated human mast cells. The inhibitory effect of LAE on the pro-inflammatory cytokine was p38 mitogenactivated protein kinase (MAPK) and nuclear factor- κ B (NF- κ B) dependent. LAE attenuated PMA plus A23187-induced degradation of I κ B α and nuclear translocation of NF- κ B, and specifically blocked activation of p38 MAPK, but not that of c-jun N-terminal kinase and extracellular signal-regulated kinase. Our findings provide evidence that LAE inhibits mast cell-derived immediate-type allergic reactions and involvement of pro-inflammatory cytokines, p38 MAPK, and NF- κ B in these effects.

Kyo E *et al.*, 1997 revealed that to examine the effect of Aged Garlic Extract (AGE) on the function of mast cells and activated T lymphocytes, we adopted the *in vitro* histamine release system, the *in vivo* IgE mediated skin reaction system and the *in*

vivo late phase reaction system. Consequently, at 1.25, 2.5, and 5.0% (v/v), AGE dose-dependantly inhibited the antigen specific histamine release by mouse anti-TNP monoclonal antibody and TNP-BSA hapten carrier complex against rat basophil cell line RBL• 2H3 by 50, 80, and 90 percent, respectively. In the IgE mediated skin reaction system, repeated or single intragastric administration of AGE (10 ml/kg), decreased by 25-45% the antigen specific ear swelling which was induced by a picryl chloride ointment applied to the ear of mice also given an intravenous administration of anti-TNP antibody IgE ascites. In the late phase reaction system, repeated or single intragastric administration of AGE (10 ml/kg) suppressed by 45-55% the antigen specific ear swelling induced by a secondary challenge to the ear of mice given a pi•cryl chloride ointment seven days prior. These results suggest that AGE application could modify, directly or indirectly, the function of mast cells, basophils and activated T lymphocytes which play a leading role in allergic cascade re•actions including inflammation.

2.2 REVIEW OF CHEWABLE TABLETS

Min Li *et al.*, 2014 showed that the root of *Scutellaria baicalensis* Georgi has been used extensively in traditional Chinese medicine for the treatment of inflammation, fever, cough, dysentery, and hypertension. Baicalein is a flavonoid isolated from the root of *Scutellaria baicalensis* Georgi and is a novel neuroprotective agent under development for the treatment of Parkinson's disease. We aimed to investigate the pharmacokinetic (PK) properties of baicalein and its main metabolite, bacalin, after single-dose administration in healthy Chinese subjects. The safety and tolerability of baicalein were also assessed. This was a Phase I, randomized, double-blind, single-dose trial of baicalein (100–2800 mg) in 72 healthy adults. Samples of blood, urine and feces were collected at regular intervals up to 48 h after administration of the

study drug. Baicalein and baicalin were then analyzed using liquid chromatography-tandem mass spectrometry (LC/MS/MS). The maximum concentration that the drug achieved after dosing (C_{\max}), time to C_{\max} (T_{\max}), terminal half-life ($t_{1/2}$), area under the curve from time zero to time of last quantifiable concentration ($AUC_{(0, t)}$), area under the curve from time zero to infinity ($AUC_{(0, \infty)}$), apparent total plasma clearance (CL/F), and apparent total volume of distribution (V/F) were determined using non-compartmental models. Dose proportion was tested using a method combining the equivalence criterion and power model. Physical examinations, vital signs, ECG findings, hematology, and urinalysis were monitored before and at regular intervals after administration of the study drug. The PK profile of baicalein and baicalin was characterized by a median T_{\max} of 0.75–3.5 h and 0.5–3 h, respectively, followed by a multiphasic profile with a $t_{1/2}$ of 1.90–15.01 h and 4.22–10.80 h, respectively. The estimates of the proportionality coefficient (90% CI) for C_{\max} , AUC_{0-t} , $AUC_{0-\infty}$ were 0.83 (0.70–0.96), 0.91 (0.81–1.00) and 0.92 (0.82–1.02), respectively. All values overlapped within the pre-specified range of (0.89–1.11), (0.93–1.07), and (0.93–1.07), respectively. Dose proportionality was inconclusive for a baicalein dose range of 100–2800 mg. The total urinary clearance of baicalein and baicalin was < 1%. Approximately 27% of baicalein was eliminated as unchanged drug in feces. Baicalein was well tolerated. Eleven treatment-related adverse events were observed, and all were rated as “mild” and resolved without further treatment. No serious adverse events occurred. Single oral doses of 100–2800 mg of baicalein were safe and well tolerated by healthy subjects. Clinical laboratory assessments showed no signs of toxicity in the liver or kidney. The favourable safety profile and PK properties warrant further clinical studies for baicalein.

Hema Chaudhary *et al.*, 2013 showed that the aim was to develop and optimize fast dissolving oro-dispersible films of Granisetron hydrochloride (GH) by two-factor, three-level Box–Behnken design as the two independent variables such as X_1 (polymer) and X_2 (plasticizer) were selected on the basis of the preliminary studies carried out before the experimental design is being implemented. A second-order polynomial equation to construct contour plots for the prediction of responses of the dependent variables such as drug release (Y_1), Disintegration time (Y_2), and Y_3 (Tensile strength) was studied. The Response surface plots were drawn, statistical validity of the polynomials was established to find the compositions of optimized formulation which was evaluated using the Franz-type diffusion cell. The designs establish the role of the derived polynomial equation and contour plots in predicting the values of dependent variables for the preparation and optimization.

Gabriel Marcelín-Jiménez *et al.*,2012 revealed that the goals of the present work were: (1) to design a specific method to quantify SIL plasma levels by using UPLC-MS/MS; (2) to compare oral SIL bioavailability in Mexican men with pharmacokinetic data in other populations; (3) to fulfil local regulatory requests; and (4) to describe the relative tolerability of a new 50-mg chewable tablet. This was a randomized, single-dose, 3-period, 6-sequence crossover study in healthy male volunteers. In each period, subjects received single oral doses of 100 mg of sildenafil (1 commercial [reference*], 1 generic [test 1 †], or 2 chewable generic tablets [test 2 ffi]), with a 4-day washout period between each dose. Serial blood samples were collected for up to 24 hours. SIL was measured in heparinized plasma by using a validated UPLC-MS/MS method. Pharmacokinetic parameters included C_{max} , AUC_{0-24} , and $AUC_{0-\infty}$. Bioequivalence was established if 90% CIs for mean test: reference ratios of log-transformed C_{max} and AUC fell within the range of 0.80 to 1.25.

Tolerability was assessed on the basis of a clinical interview with the subject and monitoring of vital signs. Demographic data showed a homogeneous population. Validation of analytical method proved to be linear within the range of 1 to 1000 ng/mL, with selectivity, accuracy, and precision. 90% CIs for test 1: reference ratios were 86.52 to 113.56, 94.75 to 108.84, and 94.97 to 108.82 for the logarithm parameters C_{max} , AUC_{0-24} , and AUC_{0-a} , respectively. The 90% CIs for the test 2:reference ratios were 82.14 to 107.24, 98.26 to 112.56, and 99.19 to 113.34 for C_{max} , AUC_{0-24} , and AUC_{0-a} . Regarding relative tolerability, slight cephalgia was the most common adverse effect. The developed analytical method was validated in compliance with local requirements and was useful for sildenafil measurement. This single-dose study under fasting conditions suggests that both test products met the Mexican regulatory criteria for assuming bioequivalence in these healthy, male Mexican volunteers. The clinical data suggest that the chewable tablets were well tolerated by volunteers.

Jinhong Wu *et al.*, 2012 revealed that the In this study, the preparation and trophic characterization of perilla chewable tablet were investigated. Perilla chewable tablet was prepared according to the following process: mixing perilla raw materials with excipients, making wet granules, drying, tableting and coating. The optimal formula was determined as follows: 8% perilla powder, 2.5% perilla extract powder, 20% isomaltooligosaccharide, 20% microcrystalline cellulose, 44.4% lactose, 0.5% essence of perilla, 0.1% sucralose, 2% erythritol, 2% vitamin C, 0.5% magnesium stearate. Results from nutrient analysis showed that perilla chewable tablet was rich in essential vitamins and mineral substances, which are good for human health.

Hiroyuki Suzuki *et al.*, 2004 showed that the aim of this study was to develop acetaminophen chewable tablets with suppressed bitterness and improved oral feeling

by examination of hard fats as the matrix base and of sweetening agents as corrigents. Witepsol H-15, W-35, S-55, E-75 and E-85, and Witocan H and 42/44 were used as hard fats. Witocan H and 42/44 were selected in view of improved oral feeling. Witocan H/Witocan 42/44 mixture tablets showed different melting characteristics and drug release rates dependent on their ratios, and those with the Witocan H/Witocan 42/44 ratio of 92.5% (w/w) and more showed good drug release. Sucrose, xylitol, saccharin, saccharin sodium, aspartame and sucralose were used as sweetening agents, and applied alone or with Benecoat BMI-40 or cocoa powder. The Witocan H tablet with 1% (w/w) saccharin plus 5% (w/w) Benecoat BMI-40 (Sc1-B5), and the Witocan H/Witocan 42/44 (92.5:7.5, w/w) mixture tablet with 1% (w/w) aspartame plus 5% (w/w) Benecoat BMI-40 suppressed bitterness and sweetness excellently, but the former tablet showed better drug release. Thus, the Witocan H tablet with Sc1-B5 is suggested as the best acetaminophen chewable tablet, exhibiting suppressed bitterness, low sweetness, improved oral feeling and good drug release.

Hiroyuki Suzuki *et al.*, 2003 reported that the various formulations with some matrix bases and corrigents were examined for development of oral chewable tablets which suppressed the bitter taste of acetaminophen, often used as an antipyretic for infants. Corn starch/lactose, cacao butter and hard fat (Witepsol H-15) were used for matrix bases, and sucrose, cocoa powder and commercial bittermasking powder mixture made from lecithin (Benecoat BMI-40) were used for corrigents against bitter taste. The bitter taste intensity was evaluated using volunteers by comparison of test samples with standard solutions containing quinine at various concentrations. For the tablets made of matrix base and drug, Witepsol H-15 best inhibited the bitter taste of the drug, and the bitter strength tended to be suppressed with increase in the Witepsol H-15 amount. When the inhibitory effect on the bitter taste of acetaminophen solution

was compared among the corrigents, each tended to suppress the bitter taste; especially, Benecoat BMI-40 exhibited a more inhibitory effect. Further, chewable tablets were made of one matrix base and one corrigent, and of one matrix base and two kinds of corrigents, their bitter taste intensities after chewing were compared. As a result, the tablets made of Witepsol H-15/Benecoat BMI-40/sucrose, of Witepsol H-15/cocoa powder/sucrose and of Witepsol H-15/sucrose best masked the bitter taste so that they were tolerable enough to chew and swallow. The dosage forms best masking bitter taste showed good release of the drug, indicating little change in bioavailability by masking.

Matthew P. Mullarney *et al.*, 2003 revealed that the physical, flow, and mechanical properties of four common pharmaceutical sweeteners were measured to assess their relative manufacturability in solid dosage formulations. Sucrose, acesulfame potassium (Sunett), saccharin sodium, and aspartame were evaluated to determine significant differences in particle shape, size distribution, and true density. Powder flow and cohesivity as well as compact mechanical properties such as ductility, elasticity, and tensile strength were measured and found to be noticeably different. Among these sweeteners, sucrose and acesulfame potassium demonstrated excellent flow ability and marginal mechanical property performance relative to over 100 commonly used pharmaceutical excipients evaluated in the authors' laboratory. Saccharin sodium and aspartame demonstrated poor flow ability and superior compact strength relative to sucrose and acesulfame, despite their noticeably higher brittleness. These data suggest that careful selection of an appropriate sweetener is warranted in obtaining desirable process and tableting robustness, particularly if sweetener loading is high. Detailed descriptions of each material property and recommendations for sweetener selection in formulation development are included.

Andreas M. Abend *et al.*, 2003 showed that the A new method for monitoring ivermectin content in HEARTGARD CHEWABLES has been developed and validated. The method consists of the automated extraction of ivermectin from the meat-based formulation under conditions of elevated temperature and pressure (accelerated solvent extraction, ASE), and determination of the active by reverse-phase high performance liquid chromatography (HPLC). The method resolves both active species of ivermectin (components H₂B_{1a} and H₂B_{1b}) from the formulation matrix.

Zhongming Liang *et al.*, 2002 reported that the A photometric titration method was developed and validated to quantitate sodium chondroitin sulfate in raw materials and Cosequin DS chewable tablet. About 0.1% (w/v) cetylpyridinium chloride was used to titrate sodium chondroitin sulfate with photometric indication at wavelength 420 nm. The standard curves for sodium chondroitin sulfate showed linearity ($r \geq 0.99$) over the selected concentration range from 0.6 to 1.4 mg/ml. The chewable tablet was ground to fine powder and extracted with water and the resulting solutions filtered through a 0.45 μ m membrane filter. Recovery between 97 and 103%. The intra- and inter- day precision as indicated by the relative standard deviation (R.S.D.) were not greater than 0.33 and 0.78%, respectively. The method was found to be specific and with excellent linearity, accuracy and precision and is well suited for the quantitation of sodium chondroitin sulfate in raw material and Cosequin DS chewable tablet.

Bruce D Anderson *et al.*, 2000 reported that the iron is the one of the leading causes of pediatric poisoning deaths in the United States. Most cases of serious iron overdose reported in the medical literature have resulted from adult formulations of iron. To begin evaluating the possibility that differences in toxicity exist between iron

preparations, we performed a retrospective evaluation of all exposures to pediatric and adult iron products reported to the American Association of Poison Control Centers" (AAPCC) Toxic Exposure Surveillance System (TESS) from 1983 to 1998. We attempted to determine the incidence of fatal iron poisoning for each group. A total of 195,780 ingestions of children"s vitamins containing iron were reported to the TESS between 1983 and 1998 with no resulting fatalities. During the same twelve-year study period, 147,079 exposures to adult forms of iron were reported with 60 fatalities ($p < 0.0001$). A prospective study is required to assess whether differences may exist in the toxicity of these two iron preparations.

Christy S. Scott *et al.*, 1999 revealed that the objectives of this study were to compare the pharmacokinetic parameters of ibuprofen administered as a suspension, chewable tablet, or tablet in children with cystic fibrosis and to determine the optimal blood sampling times for measuring ibuprofen peak concentrations. A single oral 20 mg/kg dose of ibuprofen was administered, and blood samples were obtained at 15, 30, 45, 60, 120, 240, and 360 minutes after the dose was administered. Peak plasma concentration (C_{max}) time to peak concentration (T_{max}) and other pharmacokinetic parameters were determined and compared (analysis of variance and analysis of covariance). Thirty-eight children were included (22,4, and 12 in the suspension, chewable tablet, and tablet groups, respectively). T_{max} was the only parameter for which statistical differences were noted (suspension vs tablet, $P \leq .02$). After age and sex were removed as potential confounding variables, T_{max} remained statistically different ($P \leq .001$). A 20 mg/kg dose of ibuprofen suspension is recommended, with blood samples for pharmacokinetic analysis obtained 30, 45, and 60 minutes after the dose is administered. Obtaining the first blood sample 1 hour after dose

administration will miss -90% of peak concentrations. increasing the likelihood of overdosing.

2.3 REVIEW OF BI LAYERED TABLETS

Masahiro Niwa *et al.*, 2013 reported that the layer separation is a critical defect in many bilayer tablets. Despite its importance for product quality, few studies have investigated its root cause. We evaluated bilayer tablets with varying layer separation tendencies using terahertz pulsed imaging (TPI) in comparison with other analytical methods such as tensile strength measurements, friability testing, scanning electron microscopy (SEM), and X-ray computed tomography (XRCT). The layer separation risk was determined by friability testing and shown to be correlated with the final compression pressure used for bilayer tablet fabrication. TPI could non-destructively detect cracks between the component layers that lead to layer separation. The adhesion integrity of the interface was quantified by the interface index, a unique value derived from the time-domain terahertz waveform. The interface index showed good correlation to the layer separation tendency and could distinguish interface quality among seven batches of bilayer tablets. In contrast, SEM and XRCT detected structural defects but could not distinguish batches with high or low layer separation risk. TPI revealed the relationship between compression pressure and interface quality. Thus, TPI can aid in quality control by providing a precise estimate of the layer separation risk and robust quality of bilayer tablet development with better understanding of layer separation.

Mohana Raghava Srivalli K *et al.*, 2013 reported that the Abstract Lamotrigine is a BCS class II drug with pH dependent solubility. The bilayered gastric mucoadhesive tablets of lamotrigine were designed such that the drug and controlled release polymers were incorporated in the upper layer and the lower layer had the

mucoadhesive polymers. The major ingredients selected for the upper layer were the drug and control release polymer (either HPMC K15M or polyox) while the lower MA layer predominantly comprised of Carbopol 974P. A 2³ full factorial design was constructed for this study and the tablets were optimized for parameters like tablet size, shape, ex vivo mucoadhesive properties and unidirectional drug release. Oval tablets with an average size of 14 mm diameter were set optimum. Maximum mucoadhesive bond strength of $79.3 \pm 0.91 * 10^3 \text{ dyn/cm}^2$ was achieved with carbopol when used in combination with a synergistic resin polymer. All the tested formulations presented a mucoadhesion time of greater than 12 h. The incorporation of methacrylic polymers in the lower layer ensured unidirectional drug release from the bilayered tablets. The unidirectional drug release was confirmed after comparing the dissolution results of paddle method with those of a modified basket method. Model independent similarity and dissimilarity factor methods were used for the comparison of dissolution results. Controlled drug release profiles with zero order kinetics were obtained with polyox and HPMC K15M which reported $t_{90\%}$ at 6th and 12th hours, respectively. The f_2 value with polyox was 0.992 and that with HPMC K15M was 0.946 indicating an approximate case II transport. These two formulations showed the potential for oral administration of lamotrigine as bilayered gastric mucoadhesive tablets by yielding highest similarity factor values, 96.06 and 92.47, respectively, between the paddle and modified basket method dissolution release profiles apart from reporting the best tablet physical properties and maximum mucoadhesive strength.

Anil Chaudhary *et al.*, 2011 showed that the microporous bilayer osmotic tablet bearing dicyclomine hydrochloride and diclofenac potassium was developed using a new oral drug delivery system for colon targeting. The tablets were coated with micro

porous semi permeable membrane and enteric polymer using conventional pan-coating process. The developed micro porous bilayer osmotic pump tablet (OPT) did not require laser drilling to form the drug delivery orifice. The colon-specific biodegradation of pectin could form in situ delivery pores for drug release. The effect of formulation variables like inclusion of osmogen, amount of HPMC and NaCMC in core, amount of pore former in semi permeable membrane was studied. Scanning electron microscopic photographs showed formation of in situ delivery pores after predetermined time of coming in contact with dissolution medium. The number of pores was dependent on the amount of the pore former in the semi permeable membrane. In vitro dissolution results indicated that system showed acid-resistant, timed release and was able to deliver drug at an approximate zero order up to 24 h. The developed tablets could be effectively used for colon-specific drug delivery to treat IBS.

Fridrun Podczek, 2011 showed that the Delamination is one major problem in the production of layered tablets, yet there is little knowledge about the physical reasons for this to occur. The aim of this work was to explore the theoretical influence of thermal stresses and strains that can develop during tableting and to devise an experimental method that can be used to detect delamination tendencies in bilayered tablets. Theoretical considerations have shown that thermal stresses due to development of heat during powder compaction can result in delamination, and this effect is the more pronounced the larger the Young's modulus for the individual layer materials is. Elastic mismatch further enhances delamination tendencies. Experiments on mixed powder beams showed that there is only limited adhesion between particle surfaces of a model drug (acetylsalicylic acid) and model excipient (lactose monohydrate), indicative of limited adhesion between similar interfaces in layered

tablets. A three-point bending test was developed to determine the far field stress intensity factor for bilayered compacts. Under the test conditions employed, lactose monohydrate behaved as a brittle material, whereas acetylsalicylic acid demonstrated ductility, which resulted in considerable differences in the far field stress intensity factor values, depending on whether the excipient or the drug formed the downward facing layer during the bending test. Ductile phase toughening was observed when the drug formed the downward facing layer, and hence for bilayer tablets made from these two powders lactose monohydrate must form the downward facing layer during the test. Using the correct test configuration the far field stress intensity factor correctly predicted practically observed delamination between the two material layers. Hence, the proposed fracture mechanics approach could become a formulation tool in the development of bilayered tablets.

Fridrun Podczeck, and Emad Al-Muti, 2010 reported that the aim of this work was to determine the tensile strength of bilayered tablets made from different grades of microcrystalline cellulose. While these grades are chemically identical, they differ significantly in their particle size distribution and in their mechanical properties such as Young's modulus of elasticity. Tablets were produced in the shape of beams of similar dimensions using uniaxial compression, and solid beams made from one material only were compared with bilayered beams made from various combinations of powders. It was found that in the production of layered tablets it is important for the purpose of quality assurance and control that the upper and lower layer of the compact can be identified. Otherwise, tensile strength measurements will result in large variability depending on which layer faces upwards during the test. Both particle size and Young's modulus of elasticity influenced the overall strength of layered tablets. If the material forming the lower layer was more elastic, then the beam

strength was reduced due to tension introduced into the system, acting especially at the layer interface and potentially causing partial or complete delamination. Larger differences in the particle size of the materials forming the tablet layers resulted in an overall reduced compact tensile strength.

Anuar MS and Briscoe BJ, 2010 stated that the predilection of a bi-layered tablet to fail in the interface region after its initial formation in the compaction process reduces its practicality as a choice for controlled release solid drug delivery system. Hence, a fundamental appreciation of the governing mechanism that causes the weakening of the interfacial bonds within the bi-layered tablet is crucial in order to improve the overall bi-layered tablet mechanical integrity. This work has shown that the occurrence of the elastic relaxation in the interface region during the ejection stage of the compaction process decreases with the increase in the bi-layered tablet interface strength. This is believed to be due to the increase in the plastic bonding in the interface region. The tablet diametrical elastic relaxation affects the tablet height elastic relaxation, where the impediment of the tablet height expansion is observed when the interface region experiences a diametrical expansion.

Tamara Iosio *et al.*, 2008 showed that the aim of this work was to produce by co-extrusion–spheronization pellets with two cohesive layers, one of them containing a self emulsifying system for vinpocetine, a poorly water soluble model drug. Two layers were prepared: an inert layer of microcrystalline cellulose, lactose and water and a second one wetted with the self-emulsifying system. Different formulations of both layers were tested, evaluating the effects of formulation variables with an experimental design. The screening amongst formulations was performed preparing rod extrudates and using the extrusion profiles to assess their suitability for extrusion and to anticipate quality of the spheronized extrudates. Tubular extrudates and

Co-extrudates/spheronized pellets were then produced. Two types of bi-layered pellets were prepared: type I with the self-emulsifying system internally and the inert matrix externally, whereas type II vice versa. The pellets were characterized for sizing and shape, density, hardness, *in vitro* dissolution and disintegration and released droplets size and *in vivo* tests. Although both types of pellets demonstrated adequate morphological and technological characteristics, pellets type II revealed an improved drug solubility and *in vivo* bioavailability. These preliminary technological and pharmacokinetic data demonstrated that co-extrusion/spheronization is a viable technology to produce bi-layered cohesive self-emulsifying pellets of good quality and improved *in vivo* bioavailability.

Podczek F *et al.*, 2006 revealed that the tensile strength of model materials (dicalcium phosphate dihydrate, microcrystalline cellulose and pregelatinised starch) compacted to form tablets in the form of beams consisting of two layers of equal thickness has been determined by three-point loading. The values of the tensile strength of the materials were sometimes higher and sometimes lower than the tensile strength of beams of the same thickness composed of a single material. Correction of the values for the tensile strength of the layered beams for the differences in the elasticity of the materials in the layered tablets failed to correct for these differences, as did considering the layered beams as beams of half thickness. For a layered tablet with pregelatinised starch at the bottom and microcrystalline cellulose at the top, the value of the tensile strength recorded appeared to be that of the microcrystalline cellulose as the fracture propagated across the boundary between the layers and into microcrystalline cellulose. What appeared to be the important factor was the way the failure of the beam crossed the interface between the two layers.

Qing-Ri Cao et al., 2005 showed that the effect of incorporating pharmaceutical excipients on the *in vitro* release profiles and the release mechanism of monolithic hydroxypropyl methylcellulose (4000 cps) matrix tablets (m-HPMC tablets) in terms of mimicking the dual drug release character of bi-layered Tylenol ER tablets was studied. We also compared the *in vitro* release profiles of optimized m-HPMC matrix tablet and Tylenol ER tablet in water, pH 1.2 gastric fluid, and pH 6.8 intestinal fluid, and *in vivo* drug bio availabilities in healthy human volunteers. Acetaminophen was used as the model drug. The m-HPMC tablets were prepared using a wet granulation method followed by direct compression. Release profiles and swelling rates of m-HPMC tablets were found to be highly influenced by the types and amounts of pharmaceutical excipients incorporated. Starch 1500 (Prejel) and sodium lauryl sulfate (SLS) played a key role in determining the dissolution rate of m-HPMC tablets. Additional excipients, i.e., microcrystalline cellulose (Avicel PH101) and NaH₂PO₄ were used to tune the release profiles of m-HPMC tablets. The effect of pharmaceutical excipients on drug release from HPMC-based matrix tablets was found to be mainly due to a change in hydrophilic gel expansion and on physical interactions between the drug and HPMC. The optimized m-HPMC tablet with a balanced ratio of Prejel, SLS, Avicel PH101, and NaH₂PO₄ in the formulation showed dual release profiles in water, pH 1.2 gastric fluid, and pH 6.8 intestinal fluid *in vitro*. Dual release was defined as immediate drug release within few minutes followed by extended release over 8 h. The similarity factors of m-HPMC tablets and bi-layered Tylenol ER tablets were 79.8, 66.1, and 82.7 in water, gastric fluid and intestinal fluid, respectively, indicating the equivalence of the two release profiles. No significant *in vivo* bioavailability differences were observed in healthy human volunteers. The developed m-HPMC tablet with dual release characteristics can be

easily prepared using a conventional high-speed tablet machine and could provide an alternative to commercially available bilayered Tylenol ER tablets.

Carmen Remunan-Lopez *et al.*, 1998 revealed that the This paper describes the preparation of new buccal bilayered devices comprising a drug-containing mucoadhesive layer and a drug-free backing layer, by two different methods. Bilaminated films were produced by a casting / solvent evaporation technique and bilayered tablets were obtained by direct compression. The mucoadhesive layer was composed of a mixture of drug and chitosan, with or without an anionic crosslinking polymer (polycarbophil, sodium alginate, gellan gum), and the backing layer was made of ethylcellulose. The double-layered structure design was expected to provide drug delivery in a unidirectional fashion to the mucosa and avoid loss of drug due to wash-out with saliva. Using nifedipine and propranolol hydrochloride as slightly and highly water-soluble model drugs, respectively, it was demonstrated that these new devices show promising potential for use in controlled delivery of drugs to the oral cavity. The uncrosslinked chitosan-containing devices absorbed a large quantity of water, gelled and then eroded, allowing drug release. The bilaminated films showed a sustained drug release in a phosphate buffer (pH 6.4). Furthermore, tablets that displayed controlled swelling and drug release and adequate adhesivity were produced by in situ crosslinking the chitosan with polycarbophil.

Yaling Lee and Yie W Chien, 1995 revealed that the Several mucoadhesive devices have been developed from mucoadhesive polymers for the enhanced and controlled transmucosal delivery of LHRH through oral mucosa. The mucoadhesive devices developed are of a bilayer type, which consist of a fast-release layer containing PVP (k-30), and a sustained-release layer formulated from Carbopol 934 and PVP (k-90). They have been designed for a prolonged application onto the gingival/alveolar

mucosa for a period of up to 24 h. These oral mucosa LHRH delivery devices also contain enhancer, sodium cholate, to promote the transmucosal permeation of LHRH and stabilizer, cetylpyridinium chloride, to stabilize LHRH from degradation by the microflora. In order to simulate the *in vivo* condition, a specially designed device holder was also used to have one side of the mucoadhesive device adhering to the alveolar mucosa and the other side facing the buccal mucosa. Results from the release kinetics studies demonstrated a burst release of LHRH from the fast-release layer, which provide a rapid delivery of LHRH, and a prolonged release of LHRH from the sustained-release layer, which maintains a sustained delivery of LHRH. Permeation kinetics studies indicated that the transmucosal permeation of LHRH increases as increasing the loading dose of either LHRH or enhancer in the fast-release layer, but decreases as increasing the ratio of Carbopol 934/PVP (k-90) in the sustained-release layer. The formulation of the mucoadhesive device can be varied to achieve a specific rate of transmucosal permeation.

2.4 REVIEW OF LORATIDINE

Felix Joe V *et al.*, 2011 aimed to develop extended release tablets of pseudophedrine hydrochloride and Loratadine using hydroxy propyl methyl cellulose and sodium carboxymethylcellulose in different proportions a matrix material in core tablet and Loratadine is used as immediate release for this a film coating formula was developed, so as to provide immediate release from the zone of coating. The results of the dissolution study indicated the formulations FC – VI and FC – VII showed maximum drug release up to 12 hr, the release of the drug was found to be dependent on the relative proportions of hydroxypropylmethylcellulose and sodium carboxymethyl cellulose used in core tablet. Mathematical treatment of the *in vitro* drug release data suggests that, all the formulations best fitted into first order release

kinetics. Drug release from the matrix occurred by combination of two mechanisms, diffusion of drug from tablet matrix and erosion of tablet surface.

Lakshmi CSR *et al.*, 2011 compared the effect of subliming agents on the oral dispersible property of Cinnarizine tablets. The fundamental principle used in the development of the oral dispersible tablets by sublimation technique is to maximize pore structure of the tablets. Compressed tablets prepared using a water soluble material like mannitol, does not rapidly disperse in water since it is difficult for water to penetrate into the tablets due to their low porosity. To increase the porosity of the tablets which are prepared by direct compression using mannitol, subliming agents such as camphor, menthol, ammonium bicarbonate or thymol are to be used. A high porosity was achieved due to the formation of many pores where camphor, menthol, ammonium bicarbonate and thymol particles previously existed in the compressed mannitol tablets prior to sublimation of these subliming materials. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 25 s in the mouth. We developed a direct compression method for the formulation of cinnarizine (an anti emetic drug) tablets with high porosity which dissolves rapidly using mannitol as diluent and camphor, menthol, ammonium bicarbonate or thymol as subliming agents.

Abdul Jaleel *et al.*, 2010 in their study they have aimed on the fast dispersible tablets of Loratadine. The research was to enhance the dissolution of orally disintegrated tablets of Loratadine. Orodispersible tablets of Loratadine were prepared using different types and concentrations of superdisintegrants (Ac-Di-Sol, sodium starch glycolate, and crospovidone (CP) (at different particle size)) using direct compression method. The drug is poorly water soluble therefore to enhance the solubility and release of drug, solid dispersion of drug with PVP K30 was prepared by solvent

evaporation method. The formulas were evaluated for flow properties, wetting time, hardness, friability, content uniformity, in vivo disintegration time (DT), release profiles, and buccal absorption tests. All formulations showed satisfactory mechanical strength and friability. The results revealed that the tablets containing CP as a superdisintegrant have good dissolution profile with shortest DT. The optimized formula F9 is prepared using solid dispersion of Loratadine with PVPK30 at ratio 1:3 and 15% CP with lower particle size as a superdisintegrant and by direct compression method which shows the shortest DT and good dissolution profile with acceptable stability. It can be concluded that the orodispersible tablets of Loratadine with better pharmaceutical properties than conventional tablets could be obtained using formula F9.

Behzad Sharif Makhmal Zadeh *et al.*, 2010 aimed their study to formulate a SEDDS containing a lipophilic drug, Loratadine, and to explore the potential of carriers for such system. For opportunity to perfect formulation, full factorial design with three variables; surfactant/oil, surfactant/co-surfactant proportion and percentage of drug in two levels were used. The effects of variables on formulation characters; emulsifying efficiency, particle size, drug release and rat intestine permeability were evaluated. The results showed liquid paraffin and labrafil as oil with span 20 as surfactant and capriol as co-surfactant prepared stable emulsions with refractive index higher than acidic medium and water. The particle sizes of formulations were influenced by type of oil, in the manner that liquid paraffin induced lower particle size in the range of 0.28- 1.8 micron. The percentage of drug release after 6 hrs for labrafil and liquid paraffin were 30.87-54.26% and 31.99-61.34 respectively. Formulations prepared with liquid paraffin and labrafil demonstrated drug permeability through rat intestine 2.72 and 2.25 folds compared to control. Comparison between drug release

and *in vitro* permeability indicated that drug release from formulation after mixing with acidic condition is rate limiting for gastric absorption. In conclusion SEDDS prepared with liquid paraffin provided perfect solubility in acidic condition and increased intestinal permeability.

Kathiresan K *et al.*, 2010 developed a Loratadine chewable tablets. Administration of Loratadine through oral route is a challenge in children, who have not yet learned to swallow tablets. In this research five batches of Loratadine chewable tablet dosage form at the dose of 5 mg was formulated and evaluated. Results showed that thickness, weight variation, friability, hardness, and content uniformity of all five formulations were within the acceptance limits. But in the *in-vitro* dissolution study, formulation 1, 2 and 5 demonstrated better cumulative drug release than formulation 3 and 4. However, cumulative drug release of formulation 5 was comparable with innovator than formulation 1 and 2. Three month stability study of formulation 5 revealed that there were no significant change in physical parameters, drug content and dissolution profile. Hence the research concludes that Loratadine chewable tablets formulated using Avicel CE 15 and starch paste (Formulation 5) showed better characteristics of chewable table.

Savan R. Vachhani *et al.*, 2010 focused on the development of hydro dynamically balanced delivery system of Loratadine as a single unit floating capsules. Sustained release floating capsules for Loratadine were fabricated using drug: polymer ratio of 1:4. The hydrocolloids were used in different proportions using 32 full factorial design and formulations were prepared. These formulations were optimized on the basis of buoyancy, matrix integrity, duration of floating and *in vitro* drug release. All the nine formulations showed good buoyancy and matrix integrity. The duration of floating was more than 12 h for all formulations. *In vitro* drug release study of these

formulations indicated controlled release of Loratadine and about 90 percent drug was released at the end of 12 h.

Georgeta Pavalache *et al.*, 2010 developed a novel technique for the Loratadine determination from tablets by UV. At present, Loratadine is studied by spectrophotometry, high-performance liquid chromatography and electro spray mass spectrometry. This paper describes the development of a method for determination of Loratadine by ultraviolet spectrophotometry: Loratadine methanolic solution and complex ion tetraiodomercuriat $[HgI_4]^{2-}$ form a compound in the presence of hydrochloric acid. The 380nm maximum absorbance of the compound is proportional to its concentration in Loratadine. The experiment establishes the appropriate working conditions (reaction environment, the optimal amount of reagent, the reaction time, etc.). The advantages of this sensitive method make it an efficient way to analyze Loratadine from different types of samples.

Abul Kalam Lutful Kabir *et al.*, 2009 formulated and evaluated mouth dissolving tablet of Loratadine using a special preparation technology (pharmaburst Technology) with a super disintegrating agent (Croscarmellose sodium). Tablets were prepared by direct compression technique. The granules were evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and Hausner's ratio. The tablets were evaluated for hardness, thickness, uniformity of weight, friability, wetting time, water absorption ratio, disintegration time and drug content. In vitro release studies were performed using USP-II (paddle method) in 900ml of pH 1.2 at 50rpm. The physical properties of the prepared tablets did not show any significant variations and were found to have good physical integrity. Tablets prepared with Pharmaburst B2 and Croscarmellose sodium showed a lesser disintegration time and wetting time

of 27 ± 0.10 and 38 ± 0.13 seconds respectively. The best formulations were subjected to stability studies at $40^\circ\text{C}/75\% \text{ RH}$ for 60 days.

Shashi Kiran Mishra *et al.*, 2008 formulated a controlled release system of Loratadine to increase the residence time in stomach and to modulate the release behavior of the drug. Oil entrapped floating micro beads prepared by the emulsion gelation method were optimized by 23 factorial design and a polymer ratio of 2.5:1.5 (pectin/sodium alginate) by mass, 15% (*m/V*) of oil (mineral oil or castor oil) and 0.45 mol L⁻¹ calcium chloride solution as the optimized processing conditions for the desired buoyancy and physical stability. *In vitro* drug release in the fed state conditions demonstrated sustained release of Loratadine for 8 h, which best fitted the Peppas model with $n < 0.45$. The ethyl cellulose coating on microbeads optimized by 22 factorial design resulted in a controlled release formulation of Loratadine that provided zero-order release for 8 h.

Lars Pedersen *et al.*, 2006 examined the risk of hypospadias after exposure to Loratadine and other antihistamines during pregnancy, we conducted a population-based case-control study in four Danish counties, which account for 30% of the Danish population (~1.6 M). We obtained data on maternal use of antihistamines from prescription databases, and data on birth outcomes from the Danish Medical Birth Registry (MBR) and the Hospital Discharge Registry (HDR). A total of 65,383 male births with a full prescription history of the mother in the study period from 1989-2002 were available for analysis. Within this cohort, we identified cases with a diagnosis of hypospadias, and 10 selected controls per case without such a diagnosis (matched on birth month, gender and year of birth). We identified 227 cases of hypospadias recorded in the HDR within six months postpartum and 2270 controls. One case (0.4%) and eight (0.4%) controls were exposed to Loratadine in the first

trimester and up to 30 days before the time of conception. The adjusted odds ratio (OR) for hypospadias among users of Loratadine relative to non-users was 1.4 (95% CI: 0.2-11.2) and the corresponding OR for other antihistamines was 1.9 (95% CI: 0.7-5.7). In this study, maternal exposure to Loratadine did not appear to be associated with an increased risk of hypospadias when compared with other antihistamines, although it should be noted that the statistical precision of the risk estimates might be limited.

Capokova Z. et al., 2005 dealt with the formulation of the antihistaminic into Loratadine into hydrogels. The polymer carbopol 980 in concentrations 0.5, 0.8 and 1 % was evaluated. The aim of the study was to develop an optimal concentration of carbopol 980 for the formulation of hydrogels. The choice of optimal concentration is based on the rheological properties of hydrogel as well as the pharmaceutical availability of Loratadine from hydrogels. Obtained results imply that, from the viewpoint of a topical application, the optimal concentration of carbopol 980 for the formulation of hydrogels with Loratadine is 0.5 % w/v.

Zahirul I. KHAN M et al., 2004 in this research paper Loratadine was studied both *in vitro* and *in vivo* (in healthy humans) to classify it according to the Biopharmaceutics Classification System (BCS) in order to gain more understanding of the reasons for its highly variable nature with respect to plasma time profiles, and to determine the most appropriate dissolution test conditions for *in vitro* assessment of the release profile of the drug from solid dose forms. Based on the solubility of Loratadine determined under various pH conditions and its permeability through Caco-2 monolayers, Loratadine was classified as a Class II drug. Plasma profiles were predicted by convolution analysis using dissolution profiles obtained under various pH and hydrodynamic conditions as the input function and plasma time data obtained

from a syrup formulation as the weighting function. The predicted profiles based on dissolution studies done at gastric pH values were in reasonable agreement with the mean bio-data suggesting dissolution testing should be done at gastric pH values. However, the bio-data were highly variable and it is suggested this may be due, at least in part, to high individual gastric pH variability and dissolution occurring in the intestine on some occasions, and therefore, dissolution testing should also be done in simulated intestinal fluid.

Srećo D. Škapin and Egon Matijević, 2004 developed colloidal particles of different morphologies, including spheres, of two drugs, Loratadine and danazol, was described. In principle these particles were obtained by precipitation when nonsolvents (water or aqueous surfactant solutions) were added to ethanol solutions of the drug. In addition, procedures were developed that made it possible to use the drug particles thus obtained as cores to be then coated with either silica or aluminum (hydrrous) oxide layers. The presence of these inorganic shells was confirmed by electron microscopy, energy dispersive spectroscopy, and electrophoresis.

ZHANG Yi-Fan *et al.*, 2003 aimed to investigate the pharmacokinetics of Loratadine (LOR) and its active metabolite descarboethoxyLoratadine (DCL) in healthy Chinese subjects. The method consisted of twenty healthy Chinese male subjects received a single oral dose of LOR 20 mg. A sensitive liquid chromatography-tandem mass spectrometry method (LC/MS/MS) was used for the determination of LOR and DCL in plasma. The results showed that mean maximum concentration (C_{max}) was found (17 ± 14) $\mu\text{g/L}$ for LOR at 1.2 h and (16 ± 9) $\mu\text{g/L}$ for DCL at 1.5 h. Mean area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) was (47 ± 49) $\mu\text{g}\cdot\text{h}\cdot\text{L}^{-1}$ for LOR and (181 ± 122) $\mu\text{g}\cdot\text{h}\cdot\text{L}^{-1}$ for DCL, respectively. The apparent elimination half-life ($T_{1/2}$) of LOR was (6 ± 4) h, and that of DCL was (13.4 ± 2.6) h.

The ratios of AUC_{DCL}/AUC_{LOR} ranged from 0.36 to 54.5. The final conclusion made was that LOR was rapidly absorbed and transformed to DCL. AUC of the parent drug was extremely variable, while AUC of the active metabolite DCL was moderately variable after an oral dose of LOR to Chinese subjects.

Okan Erdogan *et al.*, 2004 reported that the study sought to determine whether adding an anti-histaminic medication, Loratadine, to anti-ischemic treatment would ameliorate or improve ischemic parameters induced by exercise stress test in patients who suffered an acute myocardial infarction. Twenty stable patients with acute inferior myocardial infarction who had a positive EST were randomly allocated into 2 groups, A and B. Patients in group A and B received a 10 mg Loratadine tablet added daily to their antiischemic regimen for 7 days during the second and third week post-event, respectively. At the end of each period they underwent an exercise stress test (EST). Exercise parameters in each group were then compared before and after Loratadine therapy. Both groups showed improvements in exercise parameters after Loratadine therapy compared to basal EST results. ST_{max} (group A: 1.9 ± 0.74 vs 0.9 ± 1.29 mm, $P = .046$; group B: 2.5 ± 0.71 vs 1.4 ± 1.17 mm, $P = .041$), ST_{lead} (group A: 3.4 ± 1.08 vs 1.5 ± 2.12 , $P = .027$; group B: 4.6 ± 1.71 vs 2.22 ± 2.25 , $P = .011$), ST_{total} (group A: 4.7 ± 2.18 vs 2.1 ± 3.11 mm, $P = .024$; group B: 7.9 ± 2.92 vs 3.33 ± 3.81 mm, $P = .005$). This study revealed that loratadine, a histamine-1 receptor blocker, improves ischemic parameters of EST when given as additive therapy to a routine anti-ischemic regimen during the sub-acute phase of myocardial infarction.

Drwis Gates *et al.*, 2000 reported that the risks associated with sedating prescriptions have been well documented. The objective of this study was to assess the side effects profile of Loratadine 10 mg qd compared to Cetirizine 10 mg qd in subjects with seasonal and/or perennial allergic rhinitis. This was a randomized, parallel group.

double-blind study of Loratadine and cetirizine in patients with seasonal and/or perennial allergic rhinitis. measuring their safety profile. An electronic diary using a Visual Analog Scale (VAS), on a scale of 0 to 10. was utilized to measure degree of wakefulness/somnolence and degree of motivation to perform activities 4 times during a working day: at 8:00am. 10:00am. noon and 3:00pm. Dosing occurred at 8:00am daily for 7 days. For each time of measurement. a 7 day mean score was computed. A total of 55 patients were enrolled: 28 patients took cetirizine and 27 patients Loratadine. As compared to the cetirizine group, the Loratadine group showed mean scores to be significantly greater for both motivation and wakefulness. The motivation to perform activities scores were similar at 8:00am. immediately post-dosing. However. there was a significant difference when measured at 10:00am ($p=.0014$). noon ($p=.001$), and 3:00pm ($p <.001$). during the working day. The sleepiness scores were also similar at 8:00am. Again, there was a significant difference between Loratadine and cetirizine when measured at 10:00am ($p=.008$), noon ($p=.001$). and 3:00pm ($p <.001$). This study shows that in patients with seasonal and/or perennial allergic rhinitis, cetirizine use leads to an increase in the degree of somnolence and a decrease in the level of motivation to perform activities when compared to using Loratadine.

Kei-ichi Koizumi *et al.*, 1997 have used a sublimation technique for manufacturing of fast disintegrating tablets. Compressed tablets of a water-soluble material, prepared using mannitol, did not rapidly dissolve in water since it is difficult for water to penetrate into the tablets due to their low porosity. To increase the porosity of the tablets which are prepared by direct compression using mannitol, have researchers developed a novel method whereby camphor, a subliming material, is removed by sublimation from compressed tablets prepared using a mixture of mannitol and

camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 s in saliva in the mouth. They developed a direct compression method for the preparation, using mannitol and camphor, of a meclizine (antidinic agent) tablet with high porosity which dissolves rapidly in saliva.

Schenkel E *et al.*, 1996 reported that a double-blind, randomized, 28-day study was conducted to compare fluticasone propionate nasal spray (FP) 200meg daily with encapsulated Loratadine (LOR) 10rag daily in the treatment of seasonal allergic rhinitis. At baseline (Day 0) and at Days 14 and 28, a 7-item questionnaire was administered to 333 patients to assess patient satisfaction with their rhinitis medication. Responses were compared across treatment groups, adjusting for baseline scores. At baseline (Day 0), of the 7 items only satisfaction with sneezing relief ($p=0.032$) was significantly different between groups. There was a significant difference in overall satisfaction at baseline between the placebo and FP groups ($p\sim 0.006$). At Day 28, patients who received FP rated their satisfaction with medication significantly higher ($p<0.05$) than did patients in the placebo group; and significantly higher for all nasal related items than the LOR and placebo groups. For eye related items there was significantly higher satisfaction both the FP and Loratadine groups versus placebo; however, there was no difference between the FP and Loratadine groups. At Day 28 the overall score ($P<0.05$) was significantly higher in the fluticasone group than in the Loratadine or placebo groups. Overall patient satisfaction with medication was highest in the fluticasone group at Days 14 and 28. Overall patient satisfaction was correlated with the clinician overall evaluation of

response to therapy, based upon patient symptoms (corr=0.702, p=0.0001). In summary, after 28 days of therapy, patients with seasonal allergic rhinitis who received FP had significantly higher satisfaction with their medication which correlated with rated efficacy.

Molet S *et al.*, 1996 revealed that the allergic inflammatory reaction is characterized by leucocyte adherence and infiltration processes which are controlled by the expression of adhesion molecules on the surface of vascular endothelium. One of the main mediators implicated in these allergic reactions is represented by histamine which has been demonstrated to activate endothelial cells (EC). Histamine induces the expression of P-selectin on the surface of endothelium and the secretion of IL-6 and IL-8. Loratidine (L), a histamine H₁-antagonist, and one of its active metabolites, descarboxyethoxylomtadine (DCL), were studied at different concentrations for their ability to reduce the histamine-induced activation of human umbilical vein EC (HUVEC). HUVEC were stimulated in the presence of histamine at 1pM, 10gM and 100gM. We assessed by an ELISA method the expression of P-selectin on EC surface, as well as cytokine production in EC 24h- culture supernatants. Our results showed that for a 100p.M- histamine stimulation, L and DCL have a similar inhibitory effect on P-selectin expression (IC₅₀=0.013p.M and 0.023gM respectively). For the same dose of histamine, a 50% inhibition of IL-6 secretion was obtained for a dose of DCL equal to 2.6picoM whereas similar effects were only reached for a higher concentration of L (0.3HM). Similar results are obtained for IL-8. These results demonstrate that both L and DCL are active to reduce the histamine-induced activation of EC. Interestingly DCL seems to be efficient at lesser concentrations especially to inhibit the cytokine secretion.

2.5 REVIEW OF PHENYLEPHRINE

Dalise Zancheta *et al.*, 2015 reported that this study aimed to evaluate the effects of Wortmannin, an inhibitor of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), on aortic hyporeactivity to Phenylephrine (Phe) and nitric oxide bioavailability associated with pregnancy in hypertensive rats. The intact aortic rings of pregnant and non-pregnant Wistar or spontaneously hypertensive rats (SHRs) were stimulated with Phe (1 nmol/L to 10 mmol/L) before and after incubation with Wortmannin (10 nmol/L, 30 min). Western blot experiments analyzed the expression of phosphorylated PI3K [p85-PI3K], Akt [p-Akt (Ser 473)] and eNOS [p-eNOS (Ser 1177)] in aorta homogenates of pregnant and non-pregnant Wistar rats or SHRs. The effect of Wortmannin (10 nmol/L) on the cytosolic concentrations of nitric oxide (NO; measured using 4,5-diaminofluorescein diacetate [DAF-2DA], 10 mmol/L), Ca^{2+} (using Fluo 3-AM, 5 μ mol/L) and reactive oxygen species (ROS; using dihydroethidium [DHE], 2.5 mmol/L) were measured fluorimetrically in freshly isolated endothelial cells. Wortmannin increases the reactivity of the aorta to Phe and decreases NO concentrations in the aortic endothelial cells of pregnant Wistar rats and SHR. The PI3/AKT/endothelial nitric oxide synthase (eNOS) pathway contributes to aortic hyporeactivity to Phenylephrine associated with pregnancy in normo- and hypertensive rats.

Hyesun Jun *et al.*, 2015 showed that the A hollow microneedle (HM) was prepared to deliver a phenylephrine (PE) solution into the anal sphincter muscle as a method for treating fecal incontinence. The goal of this study was the local targeted delivery of PE into the sphincter muscle through the perianal skin with minimal pain using hollow microneedles, resulting in the increase of resting anal sphincter pressure. PE was administered on the left and the right sides of the anus of a rat through the

perianal skin using 1.5 mm long HM. An in vivo imaging system study was conducted after injection of Rhodamine B, and a histological study was performed after injection of gentian violet. The resting anal sphincter pressure in response to various drug doses was measured by using an air-charged catheter. Anal pressure change produced by HM administration was compared with change produced by intravenous injection (IV), subcutaneous (SC) injection and intramuscular (IM) injection. The change in mean blood pressure produced by HM administration as a function of PE dose was compared with change produced by PBS injection. A pharmacokinetic study of the new HM administration method was performed. A model drug solution was localized in the muscle layer under the perianal skin at the injection site and then diffused out over time. HM administration of PE induced significant contraction of internal anal sphincter pressure over 12 h after injection, and the maximum anal pressure was obtained between 5 and 6 h. Compared to IV, SC and IM treatments, HM treatment produced greater anal pressure. There was no increase in blood pressure after HM administration of PE within the range of predetermined concentration. Administration of 800 µg/kg of PE using HM produced 0.81 ± 0.38 h of t_{max} . Our study suggests that HM administration enables local delivery of a therapeutic dose of PE to the anal sphincter muscle layer with less pain. This new treatment has great potential as a clinical application because of the ease of the procedure, minimal pain, and dose-dependent response.

Xiaofeng Xu *et al.*, 2014 revealed the aim of the present work was to develop a nasal delivery system of phenylephrine hydrochloride (PE) in spray form to make prolonged remedy of nasal congestion. The formulations contain the thermosensitive hydrogel, i.e., Poloxamer 407 (P407) and Poloxamer 188 (P188) mixtures, and mucoadhesives, i.e., e-polylysine (e-PL) and low molecular weight sodium

hyaluronate (MW 11,000 Da). The *in vitro* characterizations of formulations including rheology studies, texture profiles and *in vitro* mucoadhesion potential were investigated after gelation temperatures measurements. The results showed that the concentration of P407 or P188 had significant influence on gelation temperature and texture profiles. The addition of mucoadhesives, though lowered the gel strength of formulations, increased interaction with mucin. After screening, two formulations (i.e., 1.0% PE/0.5% ϵ -PL/17% P407/0.5% P188 or Formulation A; and 1.0% PE/0.5% HA/17% P407/0.8% P188 or Formulation B) presenting suitable gelation temperatures ($\sim 32^{\circ}\text{C}$) were used for further studies on *in vitro* release behaviors and mucosa ciliotoxicity. Both formulations showed sustained release of PE for up to 8 h and similar toxicity to saline, the negative control. Thus, the thermosensitive and mucoadhesive PE-containing hydrogels are promising to achieve prolonged decongestion in nasal cavity.

Rajkumar Pyla *et al.*, 2014 reported that the Metformin, a widely prescribed antidiabetic drug, has been shown to reduce the risk of cardiovascular disease, including hypertension. Its beneficial effect toward improved vasodilation results from its ability to activate AMPK and enhance nitric oxide formation in the endothelium. To date, metformin regulation of AMPK has not been fully studied in intact arterial smooth muscle, especially during contraction evoked by G protein-coupled receptor (GPCR) agonists. In the present study, *ex vivo* incubation of endothelium-denuded rat aortic rings with 3 mM metformin for 2 h resulted in significant accumulation of metformin (>600 pmoles/mg tissue), as revealed by LC-MS/MS MRM analysis. However, metformin did not show significant increase in AMPK phosphorylation under these conditions. Exposure of aortic rings to a GPCR agonist (e.g., phenylephrine) resulted in enhanced AMPK phosphorylation by ~ 2.5 -

fold. Importantly, in metformin-treated aortic rings, phenylephrine challenge showed an exaggerated increase in AMPK phosphorylation by ~9.7-fold, which was associated with an increase in AMP/ATP ratio. Pretreatment with compound C (AMPK inhibitor) prevented AMPK phosphorylation induced by phenylephrine alone and also that induced by phenylephrine after metformin treatment. However, pretreatment with STO-609 (CaMKK β inhibitor) diminished AMPK phosphorylation induced by phenylephrine alone but not that induced by phenylephrine after metformin treatment. Furthermore, attenuation of phenylephrine-induced contraction (observed after metformin treatment) was prevented by AMPK inhibition but not by CaMKK β inhibition. Together, these findings suggest that, upon endothelial damage in the vessel wall, metformin uptake by the underlying vascular smooth muscle would accentuate AMPK phosphorylation by GPCR agonists independent of CaMKK β to promote vasorelaxation.

Aloysius UI *et al.*, 2012 reported that the female gender reduces the risk, but succumbs more to cardiovascular disease. The hypothesis that short term (8 weeks) Streptozotocin-induced diabetes could produce greater female than male vascular tissue reactivity and the mechanistic basis were explored. Aortic ring responses to Phenylephrine were examined in age- and sex-matched normoglycaemic/diabetic rats. The normoglycaemic male tissue contracted significantly more than the normoglycaemic female and the male/female diabetic tissues. Endothelial-denudation, L-NAME or MB reversed these differences suggesting an EDNO-cGMP dependence. 17 β -oestradiol exerted relaxant effect on all endothelium-denuded (and normoglycaemic endothelium-intact male) tissues, but not endotheliumintact normoglycaemic female. The greater male tissue contraction is attributable to absent 17 β -oestradiolmodulated relaxation. Indomethacin blockade of COX₂ attenuated male

normoglycaemic and female diabetic tissue contraction (both reversed by L-NAME), but augmented diabetic male tissue contraction. These data are consistent with the raised contractile TXA₂ and PGE₂ in normoglycaemic male and diabetic female tissues, and the relaxant PGI₂ in diabetic male (and female). The higher levels of PGI₂ in the normoglycaemic and diabetic female perhaps explain their greater relaxant response to Acetylcholine compared to the respective male. In conclusion, there is an endothelium-dependent gender difference in the effect of short term diabetes on vascular tissue reactivity which is COX mediated.

Jussi P Posti *et al.*, 2011 showed that the significant inter-individual variability exists in responses of human dorsal hand veins to activation of α -adrenoceptors. Simultaneous graded infusions of the α_1 - and α_2 -adrenoceptor agonists phenylephrine (3.66–8000 ng/min) and dexmedetomidine (0.0128–1000 ng/min) were given into dorsal veins of both hands and responses of 75 subjects were analyzed to assess whether a subject's sensitivity to phenylephrine (ED₅₀) predicts his sensitivity to dexmedetomidine. Individual ED₅₀ estimates of dexmedetomidine and phenylephrine ranged between 0.06–412 and 14.2–7450 ng/min and exhibited only a weak positive relationship ($r^2=0.074$, $P=0.018$). Finger temperature, body mass index, age and phenylephrine sensitivity together accounted for about 30% of dexmedetomidine ED₅₀ variation ($r^2=0.315$, $P=0.001$). The large inter-individual variability observed in the responses of dorsal hand veins to both α_1 - and α_2 -adrenoceptor agonists is not explained by some common factors; instead, dorsal hand vein responsiveness is separately determined for both receptor mechanisms.

Hagen Trommer *et al.*, 2010 revealed that the frequently used sympathomimetic drug phenylephrine has been studied by electrospray ionisation mass spectrometry. The stability of the adrenoceptor agonist was examined by investigations of the

pharmaceutically used salts phenylephrine hydrochloride and phenylephrine bitartrate. Photo stability has been studied by use of an irradiation equipment emitting a solar radiation spectrum. The experiments were carried out by analysis of aqueous drug solutions before and after irradiation treatment. The phenylephrine derivative with unsaturated side chain originating from the drug by loss of one water molecule has been detected as the major degradation product of both phenylephrine salts the hydrochloride and the bitartrate. Further degradation and oxidation products were detectable already in the full scan mode demonstrating a low stability of the drug. Tandem mass spectrometry and multiple stage mass spectrometry experiments enabled the establishment of fragmentation schemes of both salts for the first time. Irradiation treatment indicated that phenylephrine bitartrate is more prone to degradation than the hydrochloride because of an additional decomposition sensitivity of the tartaric acid counter ion. An interaction between phenylephrine and its counter ion degradation products via a nucleophilic addition mechanism is suggested to be the explanation for the detected ion signals after irradiation treatment of phenylephrine bitartrate.

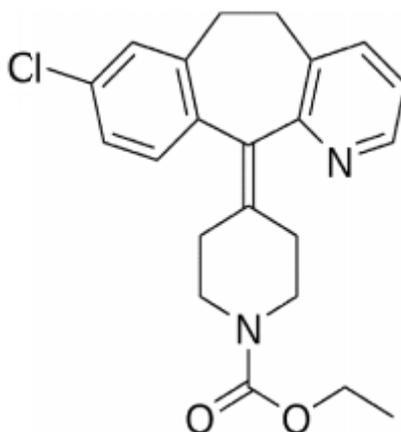
Tilo Görnemann *et al.*, 2009 revealed that the postjunctional α_2 -adrenoceptor mediating contraction of porcine pulmonary veins is of the α_{2c} -subtype. We could also demonstrate that α_1 -adrenoceptors might contribute to the contraction in that blood vessel. In the present study, we aimed at characterising the α_1 -adrenoceptor subtype(s) involved using pharmacological and molecular biological methods. In isolated rings of porcine pulmonary veins the typical α_1 -adrenoceptor agonist phenylephrine caused a concentration-dependent contraction that was inhibited by the α_{1B} -adrenoceptor selective antagonists 1-[4-(4-amino-6,7-dimethoxyquinazolin-2-yl) piperazin-1-yl]-2-[2-(isopropyl)-6-methoxyphenoxy]ethan-1-one (Rec15/2615; pA_2 8.96 \pm 0.13) and 4-

amino-2[4-[1-(benzyloxycarbonyl)-2(S)-[[1,1-dimethylethyl)amino]carbonyl]-piperazinyl]-6,7-dimethoxyquinazoline(L765,314; pA_2 7.22 ± 0.05), as well as the α_{1A} -adrenoceptor selective antagonist 8-[2-[4-(2-methoxyphenyl)-1piperazinyl]ethyl]-8-azaspiro[4.5]decane-7,9-dione (BMY7378; pA_2 8.29 ± 0.15 , slope of the Schild plot 0.75 ± 0.09 , significantly different from unity, $P < 0.05$), but not by the α_{1A} -adrenoceptor selective antagonists (\pm)-1,3,5-trimethyl-6-[[3-[4-((2,3-dihydro-2-hydroxy methyl)-1,4-benzodioxin-5-yl)-1-piperazinyl]propyl]amino]-2,4(1H,3H)-pyrimidinedione (B8805-033) and N-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro- α,α -dimethyl-1H-indole-3-ethanamine (RS-17053). These findings suggest that phenylephrine activates both α_{1B} - and α_{1D} -adrenoceptors. The observation was confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR) in porcine pulmonary veins, where mRNA signals for α_{1B} - and α_{1D} -adrenoceptors could be detected. However, the antagonist properties of rauwolscine and yohimbine (non-subtype selective α_2 -adrenoceptor antagonists) against phenylephrine showed that this agonist also activates α_2 -adrenoceptors in pulmonary veins. This was strengthened in experiments using tissues that were stimulated with forskolin (cell permeable activator of adenylyl cyclase). Phenylephrine mimicked the effect of the selective α_2 -adrenoceptor agonist UK14304 by causing an inhibition of forskolin-stimulated cAMP accumulation that was blocked by rauwolscine. It is concluded that, in addition to α_{1B} - and α_{1D} -adrenoceptors, phenylephrine can stimulate α_2 -adrenoceptors in porcine pulmonary veins.

2.6 DRUG PROFILE

2.6.1 LORATADINE

structure



Loratadine is a second-generation (Holdcroft C, 1993) H₁ histamine antagonist drug used to treat allergies. In structure, it is closely related to tricyclic antidepressants, such as imipramine, and is distantly related to the atypical antipsychotic quetiapine (Kay GG, Harris AG, 1999).

Loratadine is marketed by Schering-Plough under several trade names (e.g., Claritin) and also by Shionogi in Japan. It is available as a generic drug and is marketed for its non-sedating properties. In a version named Claritin-D or Clarinase, it is combined with pseudoephedrine, a decongestant; this makes it useful for colds, as well as allergies but adds potential side effects of insomnia, anxiety, and nervousness.

History

Schering-Plough developed Loratadine as part of a quest for a potential blockbuster drug: a non-sedating antihistamine. However, by the time Schering submitted the drug to the U.S. Food and Drug Administration (FDA) for approval, the agency had

already approved a competitor's nonsedating antihistamine, terfenadine (trade name Seldane), and, therefore, put Loratadine on a lower priority (Hall, Stephen S, 2001).

Loratadine was approved by the FDA in 1993 (Hall, Stephen S, 2001). The drug continued to be available only by prescription in the U.S. until it went off patent in 2002. It was then subsequently approved for over-the-counter sales. Once it became an unpatented over-the-counter drug, the price dropped significantly.

Schering also developed des -Loratadine (Clarinox), which is an active metabolite of Loratadine.

Indications

Loratadine is indicated for the symptomatic relief of allergy such as hay fever (allergic rhinitis), urticaria (hives), chronic idiopathic urticaria (Pons-Guiraud A *et al.*, 2006), and other skin allergies (Jasek W, 2007). For allergic rhinitis (hay fever), Loratadine is effective for both nasal and eye symptoms: sneezing, runny nose, itchy or burning eyes. Loratadine could be also used to treat mild to moderate pain from headaches.

Similarly to cetirizine, Loratadine attenuates the itching associated with Kimura's disease (Ueda T *et al.*, 2011).

Available forms

The drug is available in many different forms, such as: tablets, oral suspension, and syrup (Jasek W, 2007), and in combination with pseudoephedrine (Jasek W, 2007).

Also available are quick-dissolving tablets, which are marketed as being faster to get into one's circulatory system, but require special handling to avoid degrading in the package.

Cautions and contraindications

Patients with severe hepatic (liver) disorders may need to start with a lower dose. No dose adaptation is necessary for elderly or renally (kidney) impaired patients (Jasek W, 2007 and Mutschler Ernst *et al.*, 2001).

Loratadine is usually compatible with breast-feeding (classified category L-2 by the American Academy of Pediatrics) (Committee on Drugs, 2001). In the U.S., it is classified as category B in pregnancy, meaning animal reproduction studies have failed to demonstrate a risk to the fetus, and no adequate and well-controlled studies in pregnant women have been conducted (See Sharon, 2003).

Adverse effects

As a "nonsedating" antihistamine, Loratadine causes less (but still significant, in some cases) sedation and retardation than the older antihistamines because it penetrates the blood/brain barrier to a smaller extent. Although drowsiness is rare at the common 10-mg dose, patients should, nevertheless, be advised that it can occur and may affect performance of skilled tasks (e.g., driving). Patients who do experience drowsiness while taking Loratadine should avoid the use of alcohol, as it can cause excessive drowsiness. Otherwise, Loratadine and alcohol are unlikely to cause problems. Nevertheless, it would be in the patient's best interest to take caution when combining alcohol and any medication (Kristi Monson).

Other possible side effects include headache and antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastrointestinal disturbances (Jasek W, 2007 and Mutschler Ernst *et al.*, 2001).

Mechanism of action

Loratadine is a tricyclic antihistamine, which acts as a selective inverse agonist of peripheral histamine H₁-receptors (Mutschler Ernst *et al.*, 2001). Histamine is responsible for many features of allergic reactions.

Pharmacokinetics

Loratadine is given orally, is well absorbed from the gastrointestinal tract, and has rapid first-pass hepatic metabolism; it is metabolized by isoenzymes of the cytochrome P450 system, including CYP3A4, CYP2D6, and, to a lesser extent, several others (Nelson Wendel L *et al.*, 2002 and Ghosal A *et al.*, 2009). Loratadine is almost totally (97–99%) bound to plasma proteins. Its metabolite des-Loratadine, which is largely responsible for the antihistaminergic effects, binds to plasma proteins by 73–76% (Jasek W, 2007).

Loratadine's peak effect occurs after one to two hours, and its biological half-life is on average 8 hours (range 3 to 20 hours) with des-Loratadine's half-life being 27 hours (range 9 to 92 hours), accounting for its long-lasting effect (Affrime M *et al.*, 2002). About 40% is excreted as conjugated metabolites into the urine, and a similar amount is excreted into the feces. Traces of unmetabolised Loratadine can be found in the urine (Jasek W, 2007).

Interactions

Substances that act as inhibitors of the CYP3A4 enzyme such as ketoconazole, erythromycin, cimetidine, and furanocoumarin derivatives (found in grapefruit) lead to increased plasma levels of Loratadine. This had clinically significant effects in controlled trials of higher-than-usual doses of Loratadine (20 mg).

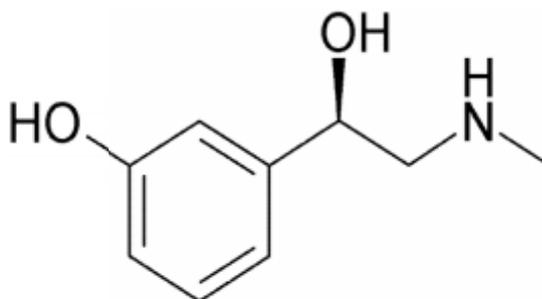
Antihistamines should be discontinued about 48 hr prior to skin allergy tests, since these drugs may prevent or diminish otherwise-positive reactions to dermal activity indicators.

Availability

Loratadine is available under many brand names and dosage forms worldwide (drugs.com , 2015). In the US, in an unprecedented action, in 1998 the insurance company Wellpoint petitioned the FDA to allow Loratadine and two other antihistamines to be made available over the counter (OTC) while it was still under patent; the FDA granted the request, which was not binding on manufacturers (Cohen JP et al., 2005). In the US, Schering-Plough made Loratadine available OTC in 2002 (Cohen JP et al., 2005). Loratadine is available in many countries OTC (AESMID, 2015).

2.6.2 PHENYLEPHRINE

Structure



Phenylephrine is a selective α_1 -adrenergic receptor agonist of the phenethylamine class used primarily as a decongestant, as an agent to dilate the pupil, and to increase blood pressure. Phenylephrine is marketed as an alternative for the decongestant pseudoephedrine, though clinical studies suggest that phenylephrine is less effective than pseudoephedrine and not more effective than placebo (Horak F *et*

al., 2009 and Day J H *et al.*, 2009). Phenylephrine can also cause a decrease in heart rate through reflex bradycardia (UCSF, 2015).

MEDICAL USES

Decongestant

Phenylephrine is used as a decongestant sold as an oral medicine or as a nasal spray. It is a common ingredient in over-the-counter decongestants. Other decongestants include oxymetazoline (Brand name: Afrin) and Pseudoephedrine (Brand name: Sudafed). Oral phenylephrine is extensively metabolized by monoamine oxidase (Drug Bank, 2015), an enzyme that is present on the outside of cells, throughout the body (Shih JC *et al.*, 2004). Compared to intravenous pseudoephedrine, phenylephrine has a reduced and variable bioavailability; only up to 38% (Drug Bank, 2015 and NZ Medicines, 2004). Phenylephrine is a sympathomimetic drug, which means that it mimics the actions of epinephrine (commonly known as adrenaline) or nor-epinephrine. Phenylephrine selectively binds to alpha receptors which cause blood vessels to constrict. Phenylephrine may cause side effects such as headache, reflex bradycardia, excitability, restlessness and cardiac arrhythmias. Phenylephrine is not suggested for use in patients with hypertension (Daily Med, 2015).

Phenylephrine is used as an alternative for pseudoephedrine in decongestant medicines due to pseudoephedrine's use in the illicit manufacture of methamphetamine. Its efficacy as an oral decongestant has been questioned, with multiple studies not being able to come to an agreement (Horak F *et al.*, 2009 and Day J H *et al.*, 2009). Whereas pseudoephedrine causes both vasoconstriction and increase of mucociliary clearance through its nonspecific adrenergic activity, phenylephrine's

selective α -adrenergic agonism causes vasoconstriction alone, creating a difference in their methods of action.

As a nasal spray, phenylephrine is available in 1% and 0.5% concentrations. It may cause rebound congestion, similar to oxymetazoline (Neo-Synephrine, 2015).

Hemorrhoids

Hemorrhoids are caused by swollen veins in the rectal area (<http://www.mayoclinic.org>). Phenylephrine can be used topically to prevent symptoms of hemorrhoids. Since phenylephrine is a vasoconstrictor, the blood vessels are narrowed, reducing the pain associated with hemorrhoids. Products for treatment may also include substances that will form a protective barrier over the inflamed area, resulting in less pain when feces is passed (phenylephrine rectal, 2015).

Mydriatic

Phenylephrine is used as an eye drop to dilate the pupil to facilitate visualization of the retina. It is often used in combination with ropivacaine as a synergist when ropivacaine alone is not sufficient. Narrow-angle glaucoma is a contraindication to phenylephrine use. As a mydriatic, it is available in 2.5% and 10% minims. Phenylephrine eye drops are applied to the eye after a topical anesthetic is applied (<http://akorn.com>).

Vasopressor

Phenylephrine is commonly used as a vasopressor to increase the blood pressure in unstable patients with hypotension, especially resulting from septic shock. Such use is common in anesthesia or critical-care practices; it is especially useful in counteracting the hypotensive effect of epidural and subarachnoid anesthetics, as well as the vasodilating effect of bacterial toxins and the inflammatory response

in sepsis and systemic inflammatory response syndrome. The elimination half life of phenylephrine is about 2.5 to 3.0 hours (Kanfer I *et al.*, 1993). The clinical effects of a single intravenous bolus dose of phenylephrine are short lived and needs to be repeated every 10–15 minutes. Commonly the drug is given as a carefully titrated intravenous infusion with a syringe pump or volumetric pump.

Because of its vasoconstrictive effect, phenylephrine can cause severe necrosis if it infiltrates the surrounding tissues. Because of this, it should be given through a central line if at all possible. Damage may be prevented or mitigated by infiltrating the tissue with the alpha blocker phentolamine by subcutaneous injection (Cooper B E, 2008).

Phenylephrine hydrochloride at 0.25% is used as a vasoconstrictor in some suppository formulations (DailyMed - PREPARATION H, 2015).

Detumescent

Phenylephrine is used by urologists to abort priapism. It is diluted significantly with normal saline and injected directly into the corpora cavernosa. The mechanism of action is to cause constriction of the blood vessels entering into the penis, thus causing decreased blood flow and relieving the priapism. An injection is given every 3–5 minutes. If priapism is not resolved in 1 hour, another form of therapy is considered (Priapism, 2015).

Side effects

The primary side effect of phenylephrine is hypertension. Patients with hypertension are typically advised to avoid products containing it. Prostatic hyperplasia can also be symptomatically worsened by use, and chronic use can lead to rebound hyperemia (Shen Howard, 2008). Patients with a history of anxiety or panic disorders, or on anticonvulsant medication for epilepsy should not take this substance. The drug

interaction might produce seizures. Some patients have been shown to have an upset stomach, severe abdominal cramping, and vomiting issues connected to taking this drug (<http://www.accessdata.fda.gov>).

Phenylephrine is pregnancy category C. Due to the lack of studies done in animals and in humans, it is not known if there is harm to the fetus. Phenylephrine should only be given to pregnant women who have a clear need (<http://www.accessdata.fda.gov>).

Because this medication is a sympathomimetic amine without beta-adrenergic activity, it does not increase contractility force and output of the cardiac muscle. It may increase blood pressure significantly to elicit a bradycardiac reflex through stimulation of vascular (likely carotid) baroreceptors (result: decrease heart rate).

A common side effect during IV administration is reflex bradycardia (Medscape, 2015).

Extended use may cause rhinitis medicamentosa, a condition of rebound nasal congestion (Neo-Synephrine, 2015).

Drug interactions

The increase in blood pressure effect of phenylephrine may be increased by drugs such as monoamine oxidase inhibitors, tricyclic antidepressants, and hydrocortisone. Patients taking these medications may need a lower dose of phenylephrine to achieve a similar increase in blood pressure.

Drugs that may decrease the effects of phenylephrine may include calcium channel blockers, ACE inhibitors and benzodiazepines. Patients taking these medications may need a higher dose of phenylephrine to achieve a comparable increase in blood pressure (Vazculep FINAL, 2015).

Substitute for pseudoephedrine

Pseudoephedrine and phenylephrine are both used as decongestants; and, until recently, pseudoephedrine was much more commonly available in the United States. This has changed because provisions of the Combat Methamphetamine Epidemic Act of 2005 placed restrictions on the sale of pseudoephedrine products to prevent the clandestine manufacture of methamphetamine. Since 2004, phenylephrine has been increasingly marketed as a substitute for pseudoephedrine; some manufacturers have changed the active ingredients of products to avoid the restrictions on sales (Hilenmeyer K, 2007). Phenylephrine has been off patent for some time, and many generic brands are available.

Effectiveness

Pharmacists Leslie Hendeles and Randy Hatton of the University of Florida suggested in 2006 that oral phenylephrine is ineffective as a decongestant at the 10-mg dose used, arguing that the studies used for the regulatory approval of the drug in the United States in 1976 were inadequate to prove effectiveness at the 10-mg dose, and safety at higher doses (Heldeles L and Hatton R, 2006).

A 2007 meta-analysis by Hatton et al concluded that the evidence for its effectiveness is insufficient (Hatton RC *et al.*, 2007), though another meta-analysis published shortly thereafter by researchers from GlaxoSmithKline found the standard 10-mg dose to be significantly more effective than a placebo (Kollar C *et al.*, 2007). In a 2007 study for the British Journal of Clinical Pharmacology, Desjardins and Berlin note that 7 studies available in 1976 support the efficacy of phenylephrine at a 10 mg dosage (Desjardins PJ & Berlin RG, 2007).

Two studies published in 2009 examined the effects of phenylephrine on symptoms of allergic rhinitis by exposing sufferers to pollen in a controlled, indoor environment. Neither study was able to distinguish between the effects of phenylephrine or a placebo. Pseudoephedrine and Loratadine-montelukast therapy were found to be significantly more effective than both phenylephrine and placebo (Horak F *et al.*, 2009 and Day J H *et al.*, 2009).

The Food and Drug Administration has stood by its 1976 approval of phenylephrine for nasal congestion as the debate continues (Hilenmeyer K, 2007).