

Abstract

In the present dissertation, efforts were applied to determine non steroidal anti inflammatory drugs in binary combinations using simple, sensitive and economic isocratic stability indicating HPLC methods. Eight stability indicating HPLC methods have been developed for the following binary combinations of the non steroidal anti inflammatory drugs i.e., i) Ketorolac Tromethamine- Gatifloxacin, ii) Ketorolac Tromethamine- Moxifloxacin Hydrochloride, iii) Ketorolac Tromethamine- Ofloxacin, iv) Ketorolac Tromethamine- Dexamethasone, v) Piroxicam- Paracetamol, vi) Naproxen Sodium- Esomeprazole, vii) Naproxen Sodium- Sumatriptan Succinate, and viii) Gatifloxacin- Flurbiprofen Sodium etc.

For combination of ketorolac and gatifloxacin a fast, sensitive and accurate stability indicating reverse phase high performance liquid chromatographic (RP-HPLC) method was developed and validated for simultaneous determination of gatifloxacin and ketorolac tromethamine in combined dosage form. Chromatographic separations were achieved on BDS Hypersil C8 column (250 X 4.6mm, 5 μm) with mobile phase consisted of methanol and phosphate buffer (pH 3.0) in the ratio of (55:45 v/v) at a flow rate of 1.5 mL min^{-1} . The analytes were detected at 270 nm using ultraviolet detection. The retention times of gatifloxacin and ketorolac tromethamine were found to be 2.460, 6.366 mins respectively. The method was linear in the concentration ranges of 30-90 $\mu\text{g mL}^{-1}$ for gatifloxacin and 50-110 $\mu\text{g mL}^{-1}$ for ketorolac tromethamine. The correlation coefficients were found to be ≥ 0.9998 and ≥ 0.9999 for gatifloxacin and ketorolac tromethamine respectively. The method resulted in good separation of both the analytes with acceptable tailing and resolution. The developed method can be used for routine determination of gatifloxacin and ketorolac tromethamine in commercial formulations.

For combination of ketorolac and moxifloxacin a simple, sensitive, specific, precise and accurate stability indicating reverse phase liquid chromatographic method was established for simultaneous determination of moxifloxacin hydrochloride and ketorolac tromethamine in bulk drugs and pharmaceutical formulations. Optimum chromatographic separations among the moxifloxacin, ketorolac and stress-induced degradation products were achieved within 13 minutes by use of BDS Hypersil C8 column (250 X 4.6 mm, 5 μm) as stationary phase with methanol and phosphate buffer pH 3.0 (55:45 v/v) as mobile phase at a flow rate of 0.7 mL min^{-1} . Detection was performed at 243 nm using diode array detector. The method was validated in accordance with ICH guidelines. Response was a linear function of concentration over the range of 20-140 $\mu\text{g mL}^{-1}$ for both analytes (correlation coefficients ≥ 0.999). The method was resulted in good separation of both the analytes and their stress induced degradation products with acceptable tailing and resolution. The peak purity index for both the analytes after all types of stress was ≥ 0.9999 indicating complete separation of both analytes peaks from the stress induced degradation products. The method can therefore be regarded as stability-indicating. The developed method can be applied successfully for simultaneous determination of moxifloxacin and ketorolac in pharmaceutical formulations and their stability studies.

For combination of ketorolac and ofloxacin a simple, specific and accurate stability indicating liquid chromatographic method was established for simultaneous determination of ofloxacin and ketorolac tromethamine in bulk drugs and pharmaceutical formulations. Optimum chromatographic separations among ofloxacin, ketorolac and stress-induced degradation products have been achieved within 15 min by using a BDS Hypersil C8 column (250 X 4.6 mm, 5 μm) as the stationary phase with methanol and phosphate buffer pH 3.0

(55 : 45 v/v) as the mobile phase at a flow rate of 0.8 mL min^{-1} . Detection was performed at 370 nm using a diode array detector. The method was validated in accordance with ICH guidelines. The response was a linear function of concentration over the range of $12\text{--}84 \mu\text{g mL}^{-1}$ for ofloxacin and $20\text{--}140 \mu\text{g mL}^{-1}$ for ketorolac tromethamine. The method resulted in excellent separation of analytes and their stress induced degradation products with acceptable tailing and resolution. The peak purity index for both the analytes after all types of stress was ≥ 0.999 indicating complete separation of both analyte peaks from the stress induced degradation products. The method can therefore be regarded as stability-indicating. The developed method can be applied successfully for simultaneous determination of ofloxacin and ketorolac in pharmaceutical formulations and their stability studies.

For combination of ketorolac and dexamethasone a simple, sensitive, specific, precise and accurate stability indicating reverse phase liquid chromatographic method was established for simultaneous determination of ketorolac tromethamine and dexamethasone in bulk drugs and pharmaceutical formulations. Optimum chromatographic separations among the ketorolac tromethamine, dexamethasone and stress-induced degradation products were achieved within 17 minutes by use of BDS Hypersil C8 column (250 X 4.6 mm, 5 μm) as stationary phase with methanol and 18 mM phosphate buffer pH 2.8 (62:38 v/v, respectively) as mobile phase at a flow rate of 1.5 mL min^{-1} . Detection was performed at 254 nm using diode array detector. The method was validated in accordance with ICH guidelines. Response was a linear function of concentration over the range of $100\text{--}700 \mu\text{g mL}^{-1}$ for ketorolac tromethamine and $10\text{--}70 \mu\text{g mL}^{-1}$ for dexamethasone (correlation coefficients ≥ 0.998). The method was resulted in good separation of both the analytes and their stress induced degradation products with acceptable tailing and resolution. The peak purity index for both the analytes after all types of stress was ≥ 0.9999 indicating complete separation of both analytes peaks from the stress induced degradation products. The method can therefore be regarded as stability-indicating. The developed method can be applied successfully for simultaneous determination of ketorolac tromethamine and dexamethasone in pharmaceutical formulations and their stability studies.

For combination of piroxicam and paracetamol a fast, simple, specific and accurate stability indicating liquid chromatographic method was described for simultaneous determination of piroxicam and paracetamol in bulk drugs and pharmaceutical formulations. Optimum chromatographic separations among the piroxicam, paracetamol and stress-induced degradation products were achieved within 6 min by using Hypersil BDS C8 column as stationary phase with acetonitrile and 0.02M phosphate buffer pH 3.0 (60:40, v/v) as mobile phase at a flow rate of 1.0 mL min^{-1} with detection using diode array detector at 254 nm. ICH guidelines were used to validate the developed method. Linearity was from $1.6\text{--}6.4 \mu\text{g mL}^{-1}$ for piroxicam and $26\text{--}104 \mu\text{g mL}^{-1}$ for paracetamol. All the analytes including the degradation products were separated with acceptable peak tailing and resolution. The peak purity index for both the analytes after all types of stress was ≥ 0.999 indicating complete separation of both analytes peaks from the stress induced degradation products. The developed method can be successfully used for simultaneous determination of piroxicam and paracetamol in pharmaceutical formulations and stability studies.

For combination of naproxen and esomeprazole a simple, economic and sensitive HPLC method was described for the concurrent determination of naproxen and esomeprazole in pharmaceutical formulations. Isocratic chromatography was performed with C-18 column and mixture of phosphate buffer (pH 6.1) and acetonitrile in ratio of (40:60, v/v) at 1.5 mL min^{-1} . The eluents were monitored at 302 nm using UV detector. The method was isocratic in

range of 9.38 to 300 $\mu\text{g mL}^{-1}$ for naproxen and 0.5 to 16 $\mu\text{g mL}^{-1}$ for esomeprazole. Validation of the method was performed by testing parameters like linearity, accuracy, precision, robustness, specificity, LOD and LOQ values. In the specificity the drugs were subjected to forced degradation studies like acidic, basic, oxidative and thermal stresses. The analytes were separated within three minutes. As the method separated the degradation products produced during forced degradation studies from the active analytes so it can be used not only for regular determination of naproxen and esomeprazole but also for stability studies.

For combination of naproxen and sumatriptan a simple, sensitive and cheap high performance liquid chromatographic method was described for the simultaneous determination of naproxen sodium and sumatriptan succinate in pharmaceutical formulations. Isocratic chromatography was performed on C-18 column using a mixture of phosphate buffer (pH 6.1) and acetonitrile in the ratio of (40:60, v/v) at a flow rate of 1.5 mL min^{-1} . The detection was carried out at a wavelength of 302 nm using UV detector. The method was linear in the concentration range of 9.38 to 300 $\mu\text{g mL}^{-1}$ for naproxen sodium and 1.7 to 54.5 $\mu\text{g mL}^{-1}$ for sumatriptan. The method was validated by performing its linearity, accuracy, precision, robustness, specificity and LOD/LOQ values. In the specificity the drugs were subjected to forced degradation studies like acidic, basic, oxidative and thermal stresses. The total eluting time for the two components was less than three minutes. As the method separated the degradation products produced during forced degradation studies from the active analytes so it can be used not only for routine determination of naproxen sodium and sumatriptan but also for stability studies.

For flurbiprofen and gatifloxacin combination a stability indicating RP-HPLC method was presented for determination of gatifloxacin and flurbiprofen in binary combination. Gatifloxacin, flurbiprofen and their degradation products were detected at 254 nm using BDS Hypersil C8 (250 X 4.6 mm, 5 μm) column and mixture of 20 mM phosphate buffer (pH 3.0) and methanol 30:70 v/v as mobile phase. Response was linear over the range of 15-105 $\mu\text{g mL}^{-1}$ for gatifloxacin ($r^2 \geq 0.998$) and 1.5-10.5 $\mu\text{g mL}^{-1}$ for flurbiprofen ($r^2 \geq 0.999$). The developed method efficiently separated the analytical peaks from degradation products (peak purity index ≥ 0.9999). The developed method can be applied successfully for determination of gatifloxacin and flurbiprofen in human serum, urine, pharmaceutical formulations, and their stability studies.