SUMMARY

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Pharmaceutical analysis is an important area of application of analytical chemistry. In pharmaceutical industry simple analytical methods are required to check the quality of raw material as well as formulation so as to meet the rigid specifications fixed by the regulatory authorities. Various analytical methods including the pharmacopoeial methods are available for the drugs which are already existing in the market. For newer drugs however, only a limited number of methods are available for analysis. The objective of the present work is to develop simple analytical technique which are sensitive accurate, rapid and relatively inexpensive and can serve as alternative to the existing methods if any.

Four drugs viz Diclofenac sodium (DFS), Diltiazem hydrochloride (DLZ), Famotidine (FMD) and Ketorolac tromethamine (KTR) were selected for the study. Analytical methods based on the most recent and rapid technique, viz Flow Injection Analysis (FIA) has been developed for all the four drugs. Sensitive and selective HPLC methods have been optimized for the analysis of DFS, DLZ and FMD. The most widely used but relatively less selective spectrophotometric methods have been developed for all the four drugs. Also simple technique like fluorimetry and titrimetry have been adapted for the determination of DLZ.

A number of simple spectrophotometric methods have been developed for the analysis of all the four drugs. The methods are based on the reaction of the drug involving oxidation, oxidative coupling, ion-pair complexation; charge transfer complexation and complexation with metal ions etc.

DFS, DLZ and FMD have been analysed based on oxidation reactions using reagents viz N-bromosuccinimide, dibromo dimethyl hydantoin. DFS was also

analysed by using oxidative reagents like ceric ammonium sulphate and potassium bromate. FMD was reacted with sodium nitrite in acidic medium in which the nitroso compound produced developed yellow colour on treatment with alkali, which was measured spectrophotometrically.

DFS was oxidised with ammonium persulphate in alkaline medium and coupled with dimethylamino benzaldehyde reagent to produce a yellow colour. In another method DFS was used to reduce iron(III) to iron(II) by heating an aqueous solution. The ferrous ion produced was made to react with 2,2'-bipyridine to form a coloured complex having λ_{max} at 520 nm. In the third method, DFS was treated with sodium hypobromite in presence of cetrimide in alkaline medium producing a yellow colour which was measured colorimetrically.

Extractive spectrophotometric methods were developed for the determination of DFS. The methods are based on formation of ion-pair complexes of the drug with reagents like acridine orange, basic fuchsin, methylene blue, safranine and toluidine blue in presence of phosphate buffer. The complexes formed were extracted into chloroform and the absorbance was measured at wavelength of maximum absorption. DLZ forms coloured ion-pair complexes with acid dyes like bromothymol blue, bromocresol green, bromocresol purple, bromophenol blue, eriochrome black T, methyl orange, picric acid, solochrome dark blue and tropaeolin OO in acidic medium. The complexes formed were quantitatively extracted in chloroform and absorbance was measured at appropriate λ_{max}. KTR was analysed by ion-pair complexation with methylene blue and safranine.

DFS forms charge transfer complexes with reagents DDQ, DCNP and iodine in nonaqueous solvent. Spectrophotemetric methods based on these reactions

were developed for the quantification of DFS. FMD has been analysed by charge transfer complexation using reagents viz chloranil, DDQ, DCNP and iodine. KTR has been determined by charge transfer complexation with DDQ and DCNP. The above methods are simple and utilize a single solvent.

DLZ forms coloured complexes with cobalt(II) thiocyanate and iron(III) thiocyanate in acidic media. The complexes formed are quantitatively extracted with benzene which showed λ_{max} at 630 nm and 495 nm respectively.

The complexation and oxidative methods described for DLZ are not suitable in presence of its degradation products. A simple and selective spectrophotometric method has been described for the determination of DLZ in tablets. The method is based on the reaction of the drug with alkaline hydroxylamine to produce hydroxamic acid, which in turn forms a purple coloured complex with ferric ion in acid medium with λ_{max} at 500 nm. The method is stability indicative as desacetyl diltiazem and acetic acid, the major degradation products do not interfere.

A spectrophotometric method has been developed based on reaction of FMD with sodium nitroprusside in alkaline medium. On acidification of solution, a red colour developed with maximum absorption at 498 nm.

Flow injection analysis has been adapted for analysis of all the four drugs. A single FIA system has been designed that is suitable for the determination of three drugs DFS, FMD and KTR. The system was assembled by utilizing various components of HPLC viz plunger pumps, six bore injector, spectrophotometric detector and a computing integrator. The drug solution in methanol were injected into a flow system containing DCNP in methanol. The colour produced due to the

formation of charge transfer complex was measured at 450 nm. Under optimum conditions sampling rate of 40 per hour was achieved with RSD less than 1.6%. In another FIA method for the determination of FMD the drug was reacted in the flow system with cupric acetate solution to form a blue coloured complex which was measured by a spectrophotemetric detector set at 314 nm or 630 nm. The samples could be analysed at rates upto 60 per hour with RSD less than 1.4 %. A FIA system has been developed for the determination of DLZ based on the colorimetric mercurothiocynate estimation of chloride counter ion. Sampling rate of 30 per hour was achieved with RSD less than 1.4 %. The benefits of the method was demonstrated in content of uniformity tests and in monitoring of dissolution studies. In spite of its limited selectivity the technique can be automated and used for batch type of analysis where a few to hundreds of samples are to be analysed.

The ability of HPLC to separate degradation products make it very useful in the analysis of pharmaceutical formulations. Reverse phase HPLC methods have been developed for the determination of DFS, DLZ and FMD in their formulation using an octadecyl silane column. For the determination of DFS mobile phase consisting of methanol and phosphate buffer was used with UV detection at 254 nm. For the determination of DLZ, mobile phase consisting of acetonitrile, methanol and phosphate buffer was used with UV detection at 240 nm. Cyproheptadine hydrochloride was used as an internal standard. A percent RSD of less than 1.5% and correlation coefficient 0.9996 were achieved over the concentration range studied. FMD was analysed by HPLC with mobile phase consisting of methanol and sodium acetate buffer and UV detection at 254 nm. The drug exhibits instability both in acidic and alklaline media. The priliminary kinetics investigation showed that degradation in acidic medium follow an apparent first

order process.

Direct fluorimetric analysis is not possible as none of the drugs selected for the study possess natural fluorescence. An indirect fluorimetric method has been developed for the estimation of DLZ in tablets by complexation with fluoregenic reagent. DLZ forms fluorescent complex with reagents like eosine yellow and erythrosine-y in acidic medium. The complexes were quantitatively extracted in chloroform and the fluorescence intensity was measured at 515 nm with excitation at 365 nm.

Simple and sensitive titrimetric methods have been proposed for the estimation of DLZ in formulation. The titration was carried out in a two phase system of water and chloroform using sodium lauryl sulphate or dioctyl sodium sulphosuccinate as titrants. Dimethyl yellow was used as indicator. The methods are stiochiometric, accurate and suitable for routine analysis of DLZ tablets.

In all, fifty one methods have been developed and validated for the analysis of four drugs and their formulations. The methods are simple, sensitive and many of them can serve as alternative to the existing methods.