ANALYTICAL METHOD DEVELOPMENT FOR SIMULTANEOUS DETERMINATION OF GLUCOSAMINE SULPHATE AND DIACEREIN FROM A MIXTURE USING DERIVATIVE AND DERIVATIVE RATIO SPECTROSCOPY

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ABSTRACT

The aim of the present work is to develop easy, fast and sensitive analytical method for the analysis of simultaneous estimation of Glucosamine sulphate (GS) & Diacerein(DC). The different concentration of GS & DC in the range of 8-40µg/mL and 2.5-20µg/mL respectively were analyzed. First derivative spectra of the mixtures containing different ratio of both the drugs were measured at 433.0 nm & 401.50 nm for GS and DC respectively. The concentration of the drugs was calculated from their corresponding regression equations measuring the intensity of the signals of the derivative ratio spectrum at 299.0 nm for GS and at 430.0 nm for DC. Limit of detection and limit of quantification for GS and DC were tested in triplicate which was found experimentally detectable. The average percent recovery was 100.58-99.46% for DC and 101.02-97.89% for GS. Percent relative standard deviation values of the methods were found within the acceptable range for both the drugs. It was observed that the deviation of the mean initial absorbance was less than 2.64% for analytical solution stability study which was within the acceptable range (±3%) indicating the stability of the analytical solutions. These methods were validated as per ICH guideline. Hence the proposed method can be used for the routine analysis of the drugs in a mixture.

Keywords: Glucosamine sulphate, Diacerein, Derivative spectrophotometry, Derivative Ratio Spectrophotometry, Method validation.

INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative disorder of multifactorial etiology characterized by loss of articular cartilage, hypertrophy of bone at the margins, subchondral sclerosis and range of biochemical and morphological alterations of the synovial membrane andjoint capsule [1]. Present day therapy for OA combines non-pharmacologic and pharmacologic treatments aimed at symptomatic relief. Although there are no medications or surgical interventions yet proven to cure OA, considerable research is currently being directed at disease modification [2].

Glucosamine is an amino sugar and a prominent precursor in the biochemical synthesis of glycosylated proteins and lipids and also major component of joint cartilage. Glucosamine supplements are widely used to prevent cartilage degeneration in the treatment of arthritis. The molecular mechanism of glucosamine was also intensely investigated. Glucosamine decreases the activity of nuclear κB (NFκB) that mediates intracellular signaling of cytokines and MMPs in stimulated chondrocytes. Glucosamine at a concentration of 10µg/ml significantly reduced IL-1ß-induced mRNA expression of c-Jun-N-terminal kinase (JNK), NOS and cyclooxygenase-2 (COX-2) that synthesizes PGE2 from arachidonic acid, in equine chondrocytes. It also suppresses the IL-1ß-induced phosphorylation of p38 mitogen-activated protein kinase (MAPK) in human synoviocytes. Glucosamine also modulates cell function. Glucosamine hydrochloride inhibited chondrocytes proliferation at a high concentration (e.g. >5mM) depending on its culture condition, however, it enhanced expression of matrix components. Glucosamine was revealed to inhibit ossification of mouse chondrogenic cells (ATDC5) and induced sulfated glucosaminoglycan by regulating chondrogenic master genes, *smad2* and *smad4.* Glucosamine has a large amount of *in-vitro* evidence that supports symptom-modifying and structure-modifying effects in clinical use [3].

Diacerein, also known as diacetylrhein an anthraquinone derivative is a symptomatic slow-acting OA drug [4]. It inhibits interleukin-1, which has demonstrated efficacy on functional manifestation of osteoarthritis and on the structural component [5]. *In-vitro* studies have shown that diacerein not only inhibits IL-1ß [6-8], but also stimulates the production of cartilage growth factors such as transforming growth factor ß, even in the presence of IL-1ß [9].

A number of studies have shown that the use of diacerein and glucosamine in combination is beneficial, because both drugs reduce symptoms and change the articular structure in OA [10].

Derivative Ratio spectrophotometric method has some reported advantages of being able to suppress matrix effects, ease of operation and obtaining results rapidly and offer greater selectivity in the simultaneous determination of two or more compounds [11-13]. Although results from this method are sometimes not as accurate as those from the HPLC method, it is still regarded as a good analytical method without prior separation to determine coexisting similar components in a simple system [14]. It is an analytical technique of good utility and offers better background correction than normal spectrophotometry for resolving binary mixtures and some ternary mixtures [15-20]. In Derivative Ratio Spectrophotometric method the spectrum for a mixture is divided by the standard spectra for each of the analyte and hence the quotient becomes a spectrum that is independent of the analyte concentration. The use of standardized spectra as divisors minimizes experimental errors and background noise. Easy measurements on separate peaks, higher values of the analytical signals and no need to work only at zero-crossing points (sometimes co-existing compounds have no maximum or minimum at these wavelengths) are advantages for derivative ratio spectrophotometry in comparison with the zero-crossing derivative spectrophotometry. Also, the presence of a lot of maxima and minima in derivative ratio spectra seems to be an advantage ,since these wavelengths give an opportunity for the determination of these compounds in the presence of other active compounds and excipients that may interfere [21].

In this method, overlap of the spectra in a certain region is desirable, because upon dividing of one spectrum by another, the error increases when one of the absorbance approaches zero [22-24]. This method permits the use of the wavelength of greatest sensitivity either at maximum or at minimum.

The review of the literature revealed that there is no Spectrophotometric method available for the combination of Glucosamine sulphate and Diacerein. Aim of present work is to develop a simple, economic, reproducible and rapid method for simultaneous estimation of this binary drug formulation.

MATERIAL AND METHODS

Chemicals and reagents

Glucosamine sulphate and Diacerein both were supplied by Bio-gen Extracts Pvt. Ltd. (Bangalore, India), Ninhydrine (AR) (Spectrochem Pvt. Ltd.) was purchased from local supplier. Phosphate buffer was prepared by USP method. Throughout the experiment we used Demineralised water.

Preparation of the drug solutions

Different concentration of glucosamine sulphate (GS) and Diacerein (DC) solutions in pH=7.4 phosphate buffer were prepared. Definite amount of 0.2% ninhydrin solution and pH=6 phosphate buffer were added to each solution. All the reaction mixtures were kept in water bath for 30 minutes, after which they were transferred to ice bath to stop the reaction and were allowed to stand at room temperature for another 10 minutes [25]. The solutions were scanned separately in the wavelength range of 200nm to 700nm. in spectrum mode. (Shimadzu UV probe 2.42 version software was used) .

First derivative Spectrophotometric method (D1)

The obtained zero order absorption spectra were

derivatized from first to fourth order. First order derivative (n=1) with $\Delta\lambda$ = 5nm spectra showed good sensitivity and linearity hence we calculated the the zero crossing wavelengths from all the spectra.

First derivative of the ratio Spectrophotometric method (RD1)

The ratio spectra of different GS standards at increasing concentrations was obtained by dividing each with the stored spectrum of the standard solution of DC (15.0µg/ml) (computer aided) are shown in [Fig. 3a] and the first derivative of these spectra traced with the interval of $\Delta\lambda$ = 5nm were illustrated in [Fig. 3b]. When the $\Delta\lambda$ values increases, the signal amplitude decreases slightly; $\Delta\lambda$ =5 nm was considered to be the optimum value. The ratio and derivative ratio spectra of the solutions of DC at different concentrations traced with the interval of $\Delta\lambda$ = 5nm by using the standard spectrum of GS (20.0 µg/ml) as divisor (computer aided), were demonstrated in [Fig. 4a] and [Fig. 4b], respectively. Divisor concentrations of both GS and DC were optimum in terms of sensitivity, repeatability and signal to noise ratio.

Assay of GS and DC mixture

The absorption spectrum was recorded for the laboratory prepared mixtures, against water as blank. The mixtures were analyzed by the developed D1 and RD1 methods.

For the simultaneous determination of GS and DC by the proposed method, it was necessary to study the influence of the variables: concentration of the standard spectrum divisor, number of points for the smoothing function and the $\Delta\lambda$ for measuring the first derivative of the ratio spectra.The influence of these different parameters was studied to optimize the signal of the derivative ratio spectra; i.e., to give good selectivity and higher sensitivity in the determination. Medium scan speed was chosen throughout the work.

Validation of the method

Linearity : Spectrophotometric analysis of GS & DC were performed in the range of 8-40µg/mL and 2.5-20 µg/mL respectively. The limit of detection (LOD) and limit of quantification (LOQ) were determined by 3.3 s/s and 10 s/s criteria respectively; where s is the standard deviation of the analytical signal and s is the slope of the corresponding calibration curve.

Accuracy : Accuracy of the method was determined by percent recovery method. The percent recovery of the added pure drugs was calculated as;

% Recovery = ((Dt-Ds)/Da) X 100;

where Dt is the total drug concentration measured after standard addition; Ds is the drug concentration in the formulation mixture; Da is the drug concentration added.

Precision: Intraday and Interday precision of the proposed methods were determined and percent relative standard deviation (%RSD) was calculated.

Stability of the analytical solution : This was evaluated by comparing the values of the freshly prepared drug solutions and the same solution after 24 hrs.

RESULTS AND DISCUSSION

Derivative method

The absorption (zero-order) UV spectra of GS & DC are shown in the figure. They exhibited UV absorption with maxima at 431nm and 402 nm for DC & GS respectively. So, the absorption spectra of GS and DC are strongly overlapped over the range of 402-431 nm (Fig. 1). The zero order spectrum of the mixture shows that GS can be quantified (with more or less accuracy) from the mixture but DC cannot be determined from this spectrum. So we have to opt for these D1 and RD1 method.

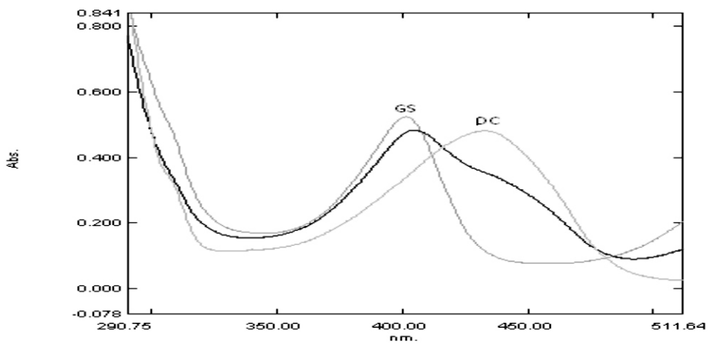

Figure 1: zero order spectrum for GS, DC & mixture of GS and DC

First derivative Spectrophotometric method (D1)

The first derivative spectra of both GS and DC (Fig. 2a & 2b) are shown below. The zero-crossing method is the most common procedure for conducting analytical calibration in derivative spectrophotometry, so 433.0 nm and 401.50 nm of the spectra were selected as zero crossing wavelengths for analysis of GS & DC respectively.

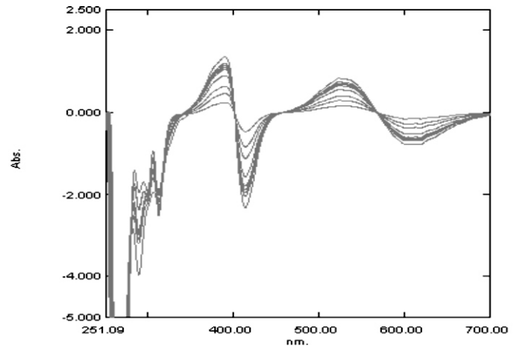

Figure 2a. First derivative UV absorption spectra Of Glucosamine sulphate KCl

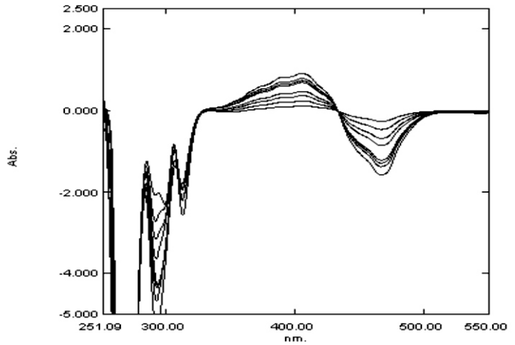

Figure 2b. First derivative UV absorption spectra of Diacerein

First derivative of the ratio spectra (RD1)

Figure 3a & 3b show the ratio spectra of different concentrations of GS (spectra divided by the spectrum of a 15.0µg/mL of DC) and DC (spectra divided by the spectrum of a 20.0µg/mL of GS) while, Figure 4a & 4b show their first derivatives. The concentration of the drugs was calculated from their corresponding regression equations measuring the intensity of the signals of the derivative ratio spectrum. Wavelength 299.0 nm (maxima) was selected for the quantification of GS in GS+DC mixture. Again wavelength 430.0 nm (maxima) was selected for the quantification of DC in DC+GS mixture. Measured analytical signals at these wavelengths were proportional to the concentrations of these drugs.

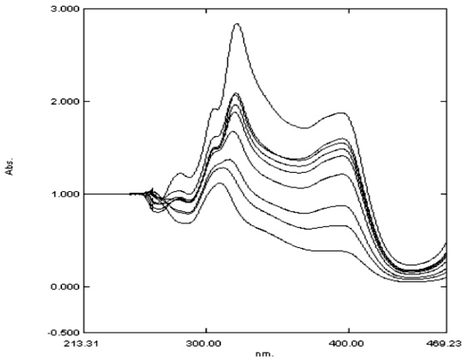

Figure 3a. Ratio spectrum of GS

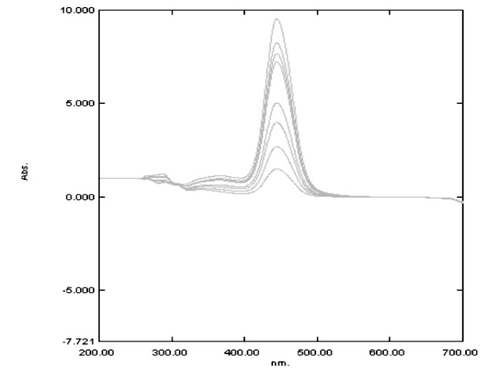

Figure 3b. Ratio spectrum of DC

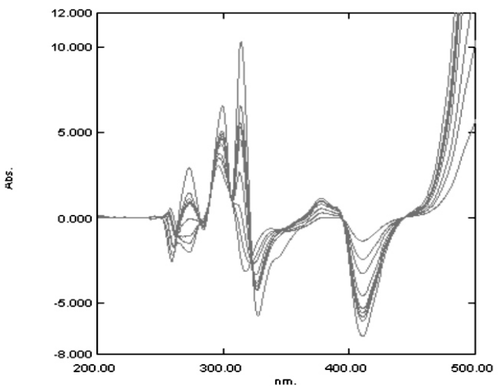

Figure 4a. First Derivative Ratio spectra of Glucosamine sulphate KCl

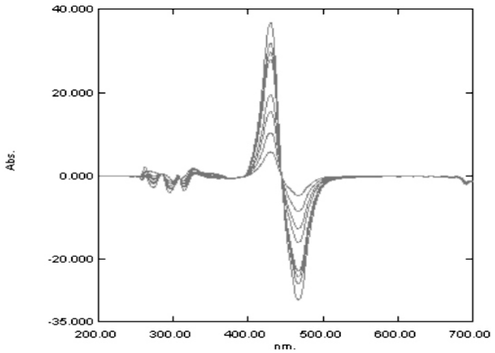

Figure 4b. First Derivative Ratio spectra of Diacerein

Statistical analysis of results

Concentration ranges and calibration graphs

A critical evaluation of the proposed Derivative and Derivative Ratio Spectrophotometric methods was performed by statistical analysis of the experimental data. Concentration range(µg/mL), Wavelength (nm), Correlation coefficient (R^2), Slope, Intercept , LOD , LOQ and percentage relative standard deviation (%RSD) of Intraday & Interday precision are given in table 1.The linearity of the calibration graphs and the adherence of the system to Beer's law were validated by the high values of the correlation coefficients and the small intercepts. Detection and quantification limits of the two drugs using the proposed methods were calculated and were verified and they were found experimentally detectable. %RSD values of the developed methods do not exceed 2% which demonstrates the good precision and repeatability of the developed methods [26].

Table 1: Validation parameters for first and ratio first derivative spectroscopic methods

Parameters assessed	Method D1		Method RD1	
	GS	DC	GS	DC
Concentration range(µg/mL)	8-40	2.5-20	8-40	2.5-20
Wavelength (nm)	433	401.50	299.0	430.0
Correlation coefficient (R^2)	0.975	0.999	0.995	0.999
Slope	1.551	4.358	9.21	151.9
Intercept	+0.045	-0.016	+1.771	+0.483
LOD	$8.7963X10^{-3}$	$5.12X10^{-3}$	$1.2273X10^{-2}$	$6.009X10^{-3}$
LOQ	0.144	$3.692X10^{-2}$	0.175	0.0449
Intraday precision (%RSD)	0.475	0.46	0.4165	0.469
Interday precision (%RSD)	1.37	0.56	1.88	1.02

Accuracy

The basic concentration level of sample solution selected for spiking of the drugs standard solution was 1.2mg of GS and 0.375 mg of DC. Addition of standard drug solution to preanalysed sample solution at three different concentration levels (80 %, 100 % and 120 %) were within the range of linearity for both the drugs.

Table 2 : Recovery studies

Amount of base drug(mg)		Amount of pure drug added (mg)		% Recovery			
				Method D1		Method RD1	
GS	DC	GS	DC	GS	DC	GS	DC
1.2	0.375	0.96	0.300	102.06	100.5	99.50	101.01
1.2	0.375	1.2	0.375	97.27	99.6	101.80	96.71
1.2	0.375	1.44	0.45	94.32	101.64	101.77	100.68
Average				97.88	100.58	101.02	99.47
Percent relative standard deviation (%RSD)				3.906	1.01	1.305	2.405

Assay of the mixture

The proposed methods were successfully applied to the analysis of GS and DC in synthetic mixtures and results are mentioned in table 3.

Table 3: Results of Assay of Laboratory mixture by first & ratio first derivative spectroscopic methods

Weight taken (mg)		% Amount found			
		Method D1		Method RD1	
GS	DC	GS	DC	GS	DC
2.0	0.25	103.48	97.48	99.79	96.43
1.6	0.375	101.7	104.3	97.07	99.59
0.8	0.75	100.8	102.06	98.2	100.50
Average		101.99	101.28	98.35	98.84
% RSD		1.363	3.476	1.366	2.136

The Derivative and Derivative Ratio Spectrophotometric methods enhance the detectability of the minor features of the UV absorption spectrum of one of the component in the presence of other. The proposed methods were validated as per ICH guideline and LOD & LOQ for method D1 & RD1 for both the drugs were calculated and tested in triplicate. RSD values found were well within the acceptable range which indicated that these methods had good repeatability and reproducibility. Results of recovery studies showed good accuracy and reproducibility which was evident from the data as results were close to 100 % and standard deviation was low. For analytical solution stability study it was observed that the deviation of the mean initial absorbance was less than 2.64% which was within the acceptable range (±3%) indicating the stability of the analytical solutions..

CONCLUSION

The present methods were simple, rapid and sensitive for the simultaneous estimation of Glucosamine sulphate & Diacerein in bulk drugs as well as in their mixture without prior separation. Thus these methods can be considered alternative tools for the routine analysis for the mixture of the combination of the drugs.

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DEVELOPMENT AND EVALUATION OF IBUPROFEN-CALCIUM ALGINATE BEADS

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ABSTRACT

THE objective of this study was to develop a sustained release dosage form of Ibuprofen (IBP) using a natural polymeric carrier prepared in a completely aqueous environment. IBP was entrapped in calcium alginate bead prepared with sodium alginate by ionotropic gelation method using calcium chloride as a crosslinking agent. The drug was incorporated either into preformed calcium alginate gel beads (sequential method) or incorporated simultaneously during the gelation stage (simultaneous method). The beads were evaluated for particle size and surface morphology using optical microscopy and SEM respectively. Beads produced by the sequential method had higher drug entrapment. Drug entrapment in the sequential method increases with increase in $CaCl_2$ and polymer concentration but decreased with increase in drug concentration. And in the simultaneous method drug entrapment increases when polymer and drug concentration were increased and it increased to a certain extent with increase in $CaCl_2$ concentration and further increase resulted in lower drug loading. FTIR studies revealed that there is no interaction between drug and $CaCl_2$. XRD studies show that crystalline drug changed to amorphous state after formulation. Release characteristics of the IBP loaded calcium alginate beads were studied in enzyme free simulated gastric and intestinal fluid.

Key words: Sodium Alginate, Calcium alginate bead, Ibuprofen, ionotropic gelation.

INTRODUCTION

Among the most abundant natural polymers, polysaccharides are widely used in pharmaceutical dosage forms as excipients like suspending agents, emulsifying agents, tablet binders, gelling agents. With the advent of macromolecular chemistry, the use of polysaccharides has been extended towards new applications in pharmaceutical, biomedical, and agricultural fields.

Sodium alginate, a hydrophilic biopolymer obtained from brown seaweeds has been found to be highly promising with respect to drug delivery because of its high biological safety [1]. Chemically, it is a polysaccharide composed of varying proportion of D-mannuronic acid (M) and L-guluronic acid (G) residues which are arranged in MM or GG blocks interspersed with MG blocks[2]. In addition to its use as a thickening, gel forming and colloidal stabilizing agent in food and beverage industries, it as also used as binder in tablet formulation [3]. Its unique property of forming water insoluble calcium alginate gel through ionotropic gelation with Ca^{+2} ions in simple and mild conditions has made possible to encapsulate both macromolecular agents [4-6] and low molecular weight therapeutic agents[7-9]. The current uses of alginate based devices are mainly related to encapsulation of various classes of therapeutic agents.

In this study, IBP was incorporated into calcium alginate beads by sequential and simultaneous methods. The effect of polymer and $CaCl_2$ concentration and that of IBP concentration on drug entrapment (drug loading) and drug release characteristics were studied. The drug-loaded beads were also characterized using different techniques.