Formulation and *in vivo* evaluation of diclofenac sodium sustained release matrix tablet: Effect of compression force

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Abstract: In the present study, Diclofenac Sodium (DS) matrix tablets were prepared by direct compression method under different compression forces (5, 10, 15 and 20 KN), using ethylcellulose as matrix forming material. The produced tablets were characterized on the foundation of satisfactory tablet properties such as hardness, friability, drug content, weight variations and *in vitro* drug release rate. Differential scanning calorimetry (DSC), Fourier Transform Infrared (FT-IR) spectroscopy and X-ray diffraction have been used to investigate any incompatibilities of the tablet's ingredients. Additionally, in vivo bioavailability has been investigated on beagle dogs. Data obtained revealed that, upon increasing compression force the *in vitro* drug release was sustained and the T_{max} value was four hours (for formulations compressed at 15 and 20 kN) compared to the conventional voltarine® 50 tablets (T_{max} value of 2 hours).

Keywords: Diclofenac sodium, ethylcellulose, matrix tablets, direct compression, compression force, sustained release, bioavailability.

INTRODUCTION

Oral sustained-release tablets are designed to achieve effective systemic drug concentrations over an prolonged period of time, thus reaching good patient compliance and permitting a decrease of daily dose frequency (Suresh, *et al*., 2011). Matrix forming materials have gained strong confidence in formulation of oral sustained release tablets (Basak *et al*., 2008). The natural polymers like agar agar, guar gum, chitosan, xanthan gum and cashew gum have been used in matrix systems of drug delivery. Also semi–synthetic release modifiers such as hydroxypropyl methylcellulose, sodium carboxy methyl cellulose, hydroxy propyl cellulose and ethylcellulose have been potentially utilized as tablets matrix system (Colombo, 1993; Siepmann *et al*., 1999; Colombo, *et al*., 2000; Kiil and Dam, 2003). Ethylcellulose is a polymer commonly used as a polymeric coating material for prolonged drug release applications (Reza *et al*, 2003). Ethyl cellulosecoatings are used to adjust drug release patern (Sadeghi *et al*., 2001) and to increase formulations stability; for example, coating granules with ethyl cellulose inhibit oxidation. Modified-release tablet formulations may also be produced using ethyl cellulose as a matrix former (Kulvanich *et al*., 2002). Ethyl cellulose as being water insoluble polymer could be used to produce water-insoluble films (Eaimtrakarn *et al*., 2001). Higher- viscosity ethylcellulose grade tend to produce stronger and more durable films. The polymer also used for preparation of microcapsules and microspheres. Recent articles have addressed the compressibility and compatibility of ethylcellulose and its utility as a matrix former in direct compression tablets (Reza *et al*., 2003). In direct compression process, first at very low forces the particles will undergo reordering to produce a less porous structure. Secondly, the particles will reach a state where further movement could be difficult. A further increase in the applied force will make either particles fragmentation and/or deformation (Duberg and Nystrom, 1986).

Particles deformation can be elastic deformation and/or plastic. Which process prevails governed by the physical features and structure of the combining material (Nesic, 1987). Some materials are ductile and consolidate by plastic deformation, some materials are consolidate and brittle by fragmentation or fracture; while others consolidate by both plastic flow and fragmentation (Roberts and Rowe, 1987). It was reported that compression force has a dramatic consequence on the crushing strength and friability of the prepared tablets, and drug release pattern. Tablet crushing-strength and compression profiles data can offer valuable information for controlling compression forces during tabletting (Jones, 1982). Diclofenac sodium (DS) is a synthetic non-steroidal anti-inflammatory and analgesic drug. It is used for treating decongestive joint disease such as rheumatic arthritis, osteoarthritis and ankylosingspondilitis (Samani *et al.,* 2003). DS is rapidly absorbed after oral administration (Samani *et al.,* 2003).

The objective of this work was to examine the applicability of compressing polymer blend in the

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preparation of prolonged release tablets formulations by direct compression. Also to study the influence of different compression forces on physical properties, *in vitro* and *in vivo* drug release rate from the prepared tablets.

MATERIALS AND METHODS

DS (Tabuk Pharmaceutical Manufacturing Co., Kingdom of Saudi Arabia). Ketoprofen powder, (Tabuk Pharmaceutical Manufacturing Co., Kingdom of Saudi Arabia). Ethylcellulose (BDH Laboratory Supplies Poole, England). Magnesium stearate (Riedel-de-Haen, AG, Germany). Marketed commercially available enteric-coated DS tablets (Voltaren 50mg® Novartis). Methanol and acetonitrile Hiper Solv™ for HPLC (BDH, Limited, Poole, England). Hydrochloric acid (Riedel-de-Haen, AG, Germany). Tribasicphosphate octahydrate (Scharlau Chemies. A, European). Glacial acetic acid (Tabuk Pharmaceutical Manufacturing CO, Kingdom of Saudi Arabia).

Preparation of drug:polymerphysical mixture

DS and ethylcellulose (at 1: 3w/w ratio) were sieved individually through a 250µm mesh sieve and then blended in Turbula (Type S27, Erweka, Apparatebau, Germany) for 15 minutes. Batch size =0.25 kg. The resulting mixture was stored in empty bottles at room temperature until use.

Preparation of tablets

The prepared powder blend was compressed into flat tablets using Flexitap single-punch Manesty machine at 5,10, 15 and 20 kN. Tablet weight of 201 mg was containing 50 mg drug, 150 mg polymer and 2% mg magnesium stearate as lubricant.

Characterization of the prepared physical mixture

1. Content uniformity

Drug content was determined for the blend by placing an accurately weighed powder sample into a 50ml volumetric flask. Methanol was added to dissolve the drug. The content of the flask was sonicated for about 20 min at ambient temperature for complete powder dissolution. The solution then filtered using Millipore 0.45 µm filter. An aliquot of the clear filtrate was diluted and DS concentration was determined by HPLC method.

2. Bulk and tapped density determination

Bulk and tapped density were determined by cylinder method (Fonner *et al*., 1966). Two grams of the powder formulation was poured into a 10 ml graduated cylinder, and the volume was measured. The same cylinder containing the powder was then tapped from a height of approximately 2 cm against a solid surface until no measurable change in the volume was observed. Bulk and tapped densities recorded were the average of three readings.

3. Carr's index (CI) and Hausner ratio (H) determination

Hausner ratio and CI was calculated using the following equations:

H=Taped Density/Balk Density

CI=[(Taped Density-Balk Density)/Taped Density] × 100

4. Flow properties

Angle of repose was measured according to the fixed-funnel and freestanding cone technique. The calculated angle of repose was the average of three readings

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Characterization of the prepared tablets

1. Weight variation testing

The test was carried out according to the USP 30 (USP 30 USA Pharmacopeia, 2007). Ten tablets were weighed individually. The results were expressed as mean value of 10 measurements.

2. Drug content uniformity

Ten tablets from each formulation were used. Each tablet was weighed individually and crushed into a powder. An accurately weighed sample (100mg) was placed in a 50 ml volumetric flask. Methanol was added to dissolve the drug. The content of the flask was sonicated for about 20 min at ambient temperature. Five ml was filtered through 0.45 µm filter, diluted and analyzed by HPLC method.

3. Tablet thickness test

The thickness of the tablet was determined using a caliper and the result was stated as mean values of 10 measurements.

4. Friability studies

Twenty tablets were selected randomly, dusted, weighed and then placed in the friabilator, allowed to fall freely 100 times from a height of 6 inch at a speed of 25 rpm for 4 min. The tablets were then dusted again, and weighed. The weight loss due to abrasion or fracture was recorded as a percentage weight loss.

5. Tablet hardness determination

Average hardness of 10 tablets was recorded. Pharmatest Multicheck System has been used for tablets hardness measurements.

Physicochemical characterization of the physical mixture and the prepared tablets

1. Differential Scanning Calorimetry (DSC)

DSC (Shimadzu, Japan) equipped with intra-cooler, a refrigerated cooling system was used. The instrument was calibrated using indium and led. DSC analysis of excipients used, prepared formulations and corresponding physical mixture were carried out. Samples (5 mg) were heated under nitrogen atmosphere on an aluminum pan at a rate of 10°C/min over a temperature range of 0 to 350°C. An empty sealed pan has been used as a reference.

Table 1: Physical properties of DS tablets produced at different compression forces

Compression force (kN)	Weight (mg)	Thickness (mm)	Hardness (N)	Friability (%)	Tensile strength (N/cm^2)	Content uniformity (%)
5	194±2	4.5±0.1	27.4±0.5	0.96±0.10	44.5±0.8	96.0±2.5
10	203±1	4.2±0.1	59.8±0.7	0.20±0.05	97.2±0.5	97.0±1.9
15	202±1	4.1±0.2	65.4±0.5	0.11±0.01	106.4±2.5	97.4±1.5
20	205±1	3.9±0.1	78.4±0.8	0.12±0.07	127.5±1.4	98.1±1.8

Table 2: Pharmacokinetic parameters of tablets containing 50mg DC and manufactured at different compression forces

Pharmacokinetic Parameters	Tablets compression force (kN)				Commercial tablets
	5	10	15	20	
T_{max} (hr)	2±0.2	3±0.3	4±0.2	4±0.2	2±0.1
C_{max} (µ/mL)	10.5±0.9	8.9±0.9	7.7±0.2	6.9±0.2	9.4±0.2
K_{el} (hr^{-1})	0.121±0.01	0.137±0.01	0.101±0.01	0.134±0.01	0.131±0.01
$t_{1/2}$ (hr)	5.7±0.3	5.1±0.3	6.8±0.5	5.2±0.4	5.3±0.4
AUC $_{0-\infty}$ (µ. hr/mL)	58.3±3.4	54.6±2.9	54.5±3.1	56.2±2.1	55.9±2.7
Relative bioavailability	1.04	0.98	0.97	1.01	-

2. Fourier Transform Infrared (FT-IR) Spectroscopy

The FT-IR spectroscopy of drug and polymer physical mixture as well as the prepared tablets was conducted on Thermoscientific Nicolet 380 FI-IR system. Samples were prepared by the conventional potassium bromide (KBr) disc method (2mg sample in 100mg KBr) and examined in the transmission method. KBr discs were prepared at 10 tons pressure. The spectra were scanned at a resolution of 2 cm^{-1}, over frequently range from 4000 to 400 $cm^{-1.}$

3. X-ray Diffraction

X-Ray diffraction patterns of the powder were gained with x-ray diffractometer (model, manufacturer), radiation at scanning speed 2 degree per minute under voltage of 40 KV and at current of 35mA for the generator. The diffracto grams were recorded from 5º to 35º/2φ at a chart speed of 40 mm/min. Tablets were crushed and subjected to the same procedure followed in powder for DSC, FT-IR and X-ray diffraction.

In-vitro drug release studies

In vitro drug dissolved from the prepared tablets was performed for a period of 8 h via a six-station USP24 paddle rotating apparatus II (VK7000, vankel, USA) at 37± 0.5ºC and 50 rpm. In the first 2 hrs we used 750mL of 0.1N HCl with pH value of 1.2 and for the remaining 6 hr we added (to the previous medium) 250mL of 0.2M tribasic sodium phosphate octahydrate to obtain a pH value of 7.4. At predetermined time intervals, 5 ml was taken from the each dissolution vessel and substituted with fresh medium to keep the volume constant. The withdrawn samples were filtered, appropriately diluted and then analyzed by HPLC method. The dissolution studies were performed in triplicate.

STATISTICAL ANALYSIS

All results were expressed as mean values ± standard deviation (SD). The statistical analysis of dissolution data (one-way analysis of variance (ANOVA) were calculated using a computer program, Graphpad INSTAT (Version 2.04, Ralf Stahlman, Purdue University, USA, 931897S). An evidence of a significant difference was considered when $P<0.05$.

***In-vivo* study**

The purpose of the in-vivo study was to relate the pharmacokinetic parameters of the tablets produced at different compression forces. Furthermore, relative bioavailability of the prepared DS tablets was compared to the commercially available DS tablets (Voltaren® 50 tablets containing 50 mg DS).

Animals

Six male Beagle dogs weighing 12-14 kg were used in the study in accordance with a protocol approved by the Institutional Review Board-use and Care of Animal at King Saud University. The dogs were fasted for 24 h before each experiment and were not allowed to any food during the first 6 h after the first dose administration, with free access to water.

Blood sampling protocol

The prepared tablets were administered with 50 mL of water. The dog's leg was shaved and a forefoot vein was cannulated using 18 gauge cannulae. Five milliliter blood samples were withdrawn in heparinized vaccutainer tubes before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 10 h post administration. The samples were centrifuged for 10 min at 3500 rpm and plasma separated out and stored in glass containers at -20°C, until analysis.

Method of assay

A high-performance liquid chomatography (HPLC) system (Shimadzu Corporation, Kyoato, Japan) equipped with Rheodyne sampling injector with a 20µL sample loop. Samples were analyzed on reverse-phase Bondpak C_{18} column attached to a C_{18} precolumn, U.V variable wave length detector model 10AV set at 280 nm.50 µL of internal standard ketoprofin solution (10µg mL^{-1}) was added to each sample. The mobile phase consisted of acetonitrile / water (50:50 v/v), adjusted at pH value of 3.6 with glacial acetic acid. The mobile phase filtered through 0.45 µm millipore filter and degassed by ultra-sonication under vacuum and pumped at a constant rate of 2mL/min at ambient temperature.

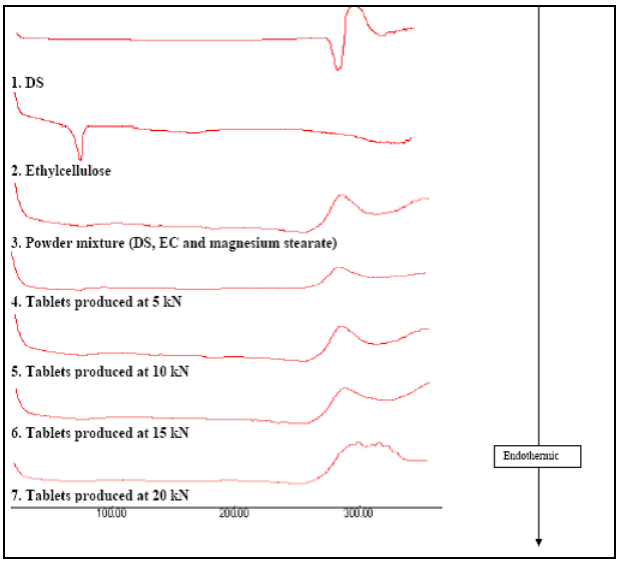

Fig. 1: DSC thermo gram of DS tablets.

Pharmacokinetic analysis

Pharmacokinetic parameters for DS tablets produced at different compression forces were determined from the plasma concentrations-time data.

STATISTICAL ANALYSIS

Data were calculated by a model-independent method using the PKA nalyst® for Windows software (Micro Math® Scientific Software, Salt Lake City, UT, USA). Calculation of the terminal elimination half-life was done by least-squares regression analysis of the terminal part of the concentrations-time curves. Areas under concentration curves (AUC) were estimated using the log-linear trapezoidal rule.

RESULTS

The flow properties of DS physical mixture were represented by CI and angle of repose. The value of angle of repose was 47.2 and CI was 44.9. Upon addition of 2% magnesium stearate angle of repose and CI was reduced to 39.7 and 37.4 respectively.

Tablet evaluation and characterization

From table 1 it could be observed that tablet friability is highly dependent upon the compression force, i.e., increasing the compression force was accompanied by a reduction of the % friability. Moreover, it was obvious that compression forces highly affect the breaking force (BF) value of the produced tablets. For example, DS tablets produced at 5kN had breaking force values of 27.4±0.5 N, while those manufactured at 20 kN showed BF value of 78.4±0.8 N. Drug content uniformity of the tested DS tablets ranged from 96% to 98% which was within the allowed limits.

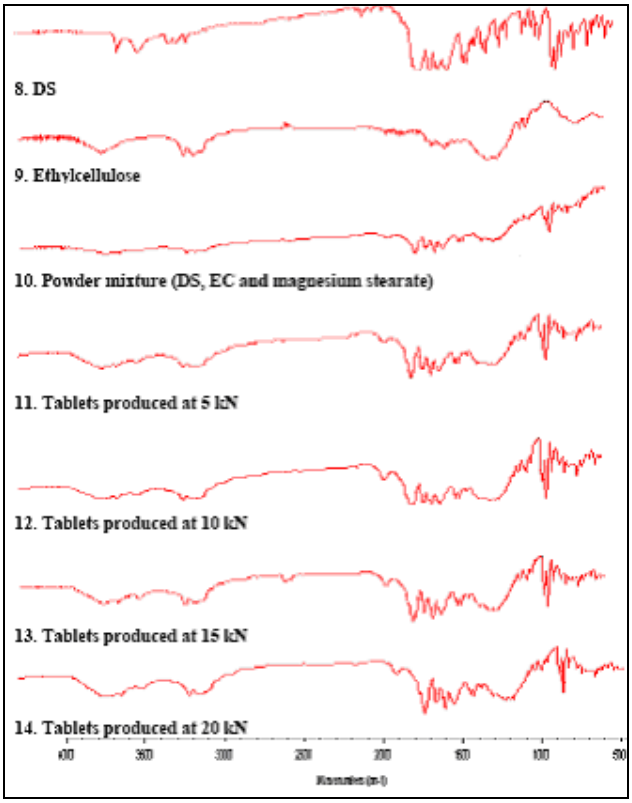

Fig. 2: IR spectra of DS tablets.

The prepared DS tablets at different forces and the corresponding physical mixture, as well as the individual components were evaluated for the possible physical and chemical interaction between ethyl cellulose and DS by the DSC and FT-IR spectroscopy.

As shown in fig. 1, the DSC thermo gram of DS showed sharp endothermic peak at 288°C with a heat of fusion (ΔH) value 20.18 joule/g as well as exothermic peak at 296°C indicated the fusion of the solvated crystals (Tudja *et al.,* 2001). It is clearly evident that increasing the

compression force during tablet manufacture resulted in pronounced increase in ΔH value of DS. It was found that ΔH values for tablets compressed at 5, 10, 15 and 20 kN were 20.18, 26.93, 50.88 and 188.82 joule/g respectively. This phenomenon could be explained on the basis that increasing compression force lowers the inter-particle spaces and so higher energy will be required to breakdown the intermolecular force (Puttipipatkhachorn *et al.,* 2005).

FT-IR spectrum of DS (fig. 2) showed that the principal IR peaks at 1280 and 1303 cm^{-1} resulted from C-N stretching and the peak at 1504 and 1572 cm^{-1} resulted from C=C stretching and C=O stretching of carboxyl ate group, respectively (Piyakulawat *et al.,* 2007). The N-H band was seen at the same region in tablet formulations as well as the physical mixture.

The X-ray powder diffraction showed that DS is present as crystalline powder due to several diffraction peaks, but the more characteristic one was seen at 6.78 A^o. This diffraction peak was seen again in case of tablets compressed at different forces as well as the corresponding physical mixture (fig. 3).

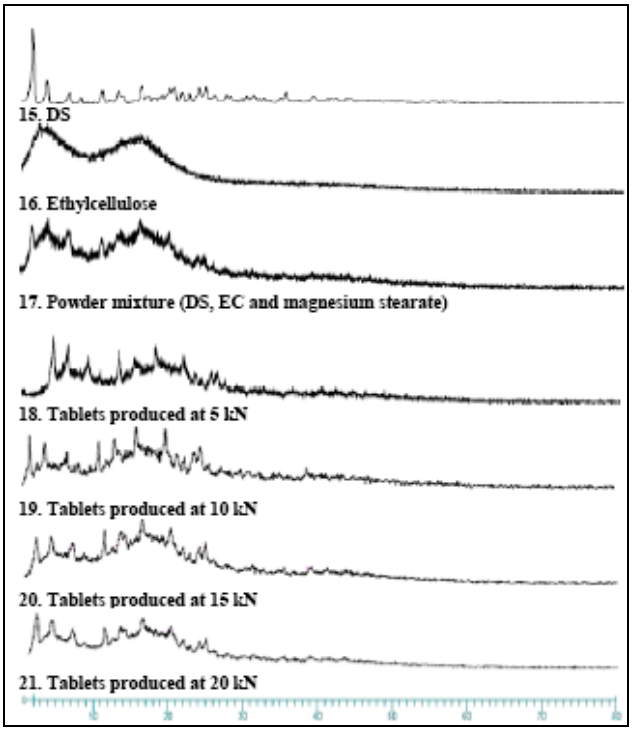

Fig. 3: X-ray IR spectra of DS tablets

The effect of compression force on the in vitro release rate of DS from EC tablets is shown in fig. 4.

In vivo evaluation of DS tablets

Fig. 5 represents the mean plasma concentration-time profiles after oral administration of DS tablet compressed at different compression forces to beagle dogs. The values of the area under plasma concentrations-time curve ($AUC_{0-\infty}$) were found to be insignificantly different ($P<0.01$) between the control and the selected matrix tablet formulations (table 2). Values of T_{max} for the prepared formula compressed at 5, 10, 15 and 20kN were found to be 2, 3, 4 and 4 respectively. The magnitude of C_{max} varied from one formula to another according to the value of compression forces. C_{max} values were 10.5µg/ml, 8.9µg/ml, 7.7µg/ml, 6.9 µg/ml and 9.4 µg/ml for tablets produces under 5, 10, 15 and 20kN as well as commercial Voltaren® 50 tablets respectively. The relative bioavailability values of DS in the studied tablets compressed at different forces and the commercial product are illustrated in table 2.

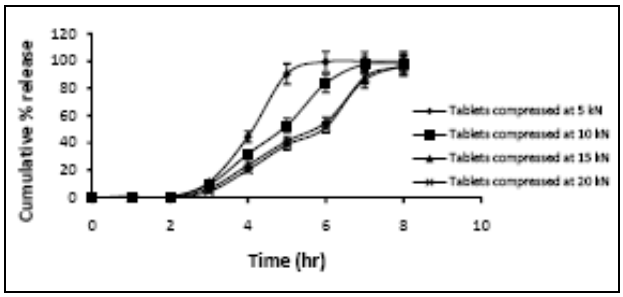

Fig. 4: DS release profile from tablets manufactured at different compression forces.

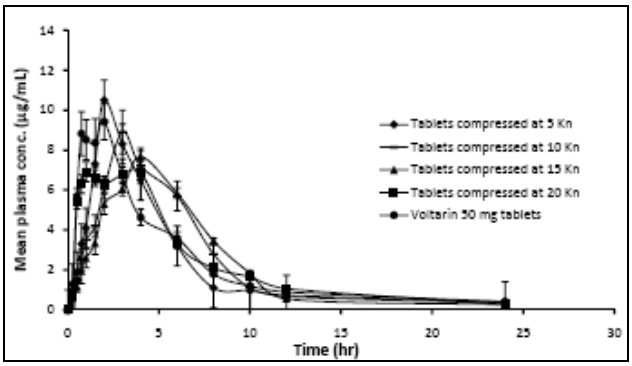

Fig. 5: Mean plasma concentration-time profiles after oral administration of tablets (50mg DC) produced at different compression forces.

PHARMACOKINETICS ANALYSIS

Pharmacokinetic parameters for DS tablets produced at different compression forces were determined from the plasma concentrations-time data.

Data were calculated by a model-independent method using the PKA nalyst® for Windows software (Micro Math® Scientific Software, Salt Lake City, UT, USA). Calculation of the terminal elimination half-life was done by least-squares regression analysis of the terminal part of the concentrations-time curves. Areas under concentration curves (AUC) were estimated using the log-linear trapezoidal rule.

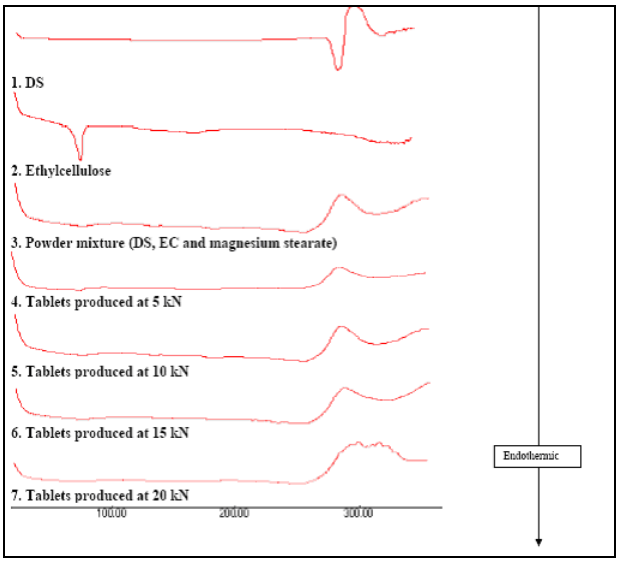

Fig. 1: DSC thermo gram of DS tablets.

DISCUSSION

The flow properties of DS physical mixture were poor. Upon addition of 2% magnesium stearate, angle of repose and CI was reduced which indicates that the flow properties was improved to acceptable range.

It was found that, increasing the compression force leads to decreasing drug release rate (Dabbagh *et al.,* 1996).

The pronounced increase in ΔH value of DS could be explained on the basis that increasing compression force lowers the inter-particle spaces and so higher energy will be required to breakdown the intermolecular force (Puttipipatkhachorn *et al.,* 2005). Increasing the compression force resulted in reduction of the rate of DS release which is due to the fact that when compression force increases, the crushing strength (hardness) increases resulting in slow drug release (Jones, 1982). In addition, the kinetic modeling of DS release revealed the prominence of zero order kinetic as a release mechanism. Furthermore, the calculated zero order release rate constant was found to be dependent on the compression force.

The disappearance of the endothermic peak might be due to the dissolving of DS in the molten polymer.

The N-H band was seen at the same region in tablet formulations as well as the physical mixture. This observation revealed the absence of any chemical interaction between ethyl cellulose and DS.

It was found that the same diffraction peak was seen again in case of tablets compressed at different forces as well as the corresponding physical mixture, which assure that the crystalline structure of DS was not affected by compression. Values of T_{max} for the prepared formula compressed at 5, 10, 15 and 20kN were found to be 2, 3, 4 and 4 respectively. The magnitude of C_{max} varied from one formula to another according to the value of compression forces. From the pharmacokinetics data it is clear that compression force has a dramatic effect on retarding DS absorption from the tested formulations.

CONCLUSIONS

Direct compression DS sustained release tablets were successfully prepared using ethyl cellulose as a matrix forming material. A confirmatory analytical technique, like DSC, IR and X-ray diffractometery, proved the physico-chemical stability of DS and the absence of any chemical interaction with the matrix-forming polymer. Increasing compression force (5, 10, 15 and 20 kN) sustained drug dissolved from the prepared matrix tablets. The study also revealed that the prepared tablets have almost the same relative bioavailability to the commercial Voltaren® 50 tablets but with sustained drug plasma concentrations up to four hours in tablets compressed at 15 and 20Kn.

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