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PREPARATION AND INVESTIGATION OF ACETYL SALICYLIC ACID – VALINE COMPLEX FOR TRANSDERMAL DELIVERY

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An acetyl salicylic acid-valine complex was prepared and evaluated for the potential transdermal application. The complex prepared by freeze-drying technique. The complex was analyzed by using differential scanning calorimetry (DSC), scanning electron microscope (SEM), ^{1}H nuclear magnetic resonance (^{1}H NMR), X-ray powder diffraction (X-RPD) and Fourier transform infrared (FTIR). The results revealed the formation of an ionic type complex between acetyl salicylic acid and valine in a molar ratio of 1:1. This study comprised formulation of the complex in different gel bases. Release studies revealed that the 7% w/w sodium alginate gel allowed highest complex release and 20%w/w pluronic F-127 showed the lowest release. Permeation studies through rat skin revealed that 0.5%w/w carpobol 934 showed the highest flux from all studies gel bases and high complex permeation compared to acetyl salicylic acid alone. The present results confirmed that acetyl salicylic acid- valine complex is a promising and safe delivery system that can be utilized for transdermal application.

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Keywords: Acetyl salicylic acid, Valine, Complexation, Gel bases, Transdermal delivery system.

1. Introduction

Acetyl salicylic acid (ASA, aspirin), (Fig. 1A) is one of the most popular drugs all over the world. The popularity of ASA is not only for its antipyretic, analgesic and anti-inflammatory effect but also for its cost-effectiveness when used for the secondary prevention of coronary artery disease [1]. The average yearly consumption of aspirin in the developing countries is 30 g per person [2]. On the other hand the United States consumed 35,000 kg ASA daily [3]. ASA has different therapeutic effects depending on the drug dose and administration pathway. Acetyl salicylic acid is the basic antiplatelet agent for all kinds of acute disease that may cause platelet-dependant thrombotic vessel occlusion[4]. As a nonsteroidal antiinflammatory drugs (NSAIDs) ASA act as nonselective inhibitors of cyclooxygenase isozymes (Coxs). This lack of selectivity has been linked to its tendency to cause gastrointestinal side effects[5]. The assumed mechanisms have included alterations in mucosal prostaglandin biosynthesis, disruption of the gastric mucosal barrier, derangements in mucus/bicarbonate secretion by gastroduodenal epithelium, and abnormalities in the microcirculation [6-8] 50–325 mg/day oral ASA is usually used for cardiovascular prophylaxis. The mechanism of the cardioprotective effect is by the irreversible inactivation of platelet Cox-1, resulting in a reduced production of the thromboxane (TXA2) [9].

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After oral administration, the bioavailability of regular ASA tablets was about 54% and terminal half life of 15.4 min [10]. A considerably lower bioavailability has been reported for enteric-coated tablets and sustained-release, microencapsulated preparations [11]. The decreased bioavailability due to its extensive presystemic hydrolysis in the gut and liver into salicylic acid which is devoid of antiplatelet activity. At the same time, Continuous exposure of new platelets to ASA is necessary to achieve prolonged inhibition of platelet aggregation[12]

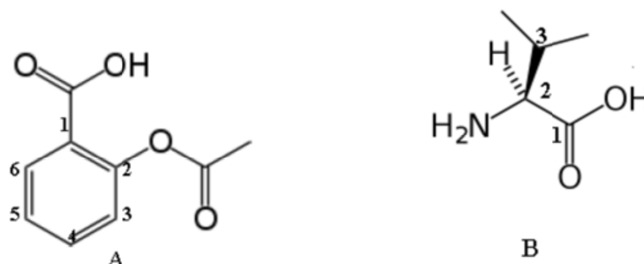


Fig.1: Chemical structure of: (A) Acetyl salicylic acid (ASA), and (B)L- Valine

Valine (Fig. 1B), [13] is an α-amino acid with the chemical formula $HO_2CCH(NH_2)CH(CH_3)_2$. L-Valine is one of 20 proteinogenic amino acids. This essential amino acid is classified as nonpolar. Human dietary sources include cottage cheese, fish, poultry, peanuts, sesame seeds, and lentils. Valine is an essential amino acid, hence, it must be ingested, usually as a component of proteins. It is synthesized in plants via several steps starting from pyruvic acid. The initial part of the pathway also leads to leucine [14]. Valine is a non-polar branched-chain amino acid (BCAA) that works with the other two BCAAs, isoleucine and leucine, to promote normal growth, repair tissues, regulate blood sugar, and provide the body with energy [15]. Valine-enriched total parenteral nutrition was found to promote mucosal growth significantly after 5-fluorouracil-induced enteritis in the rat [16]. I t was reported that valine enhances liver regeneration after a hepatectomy while also promoting the lipid metabolism in the rat [17]. Using valine a prodrug of floxuridine (5-Val-FUdR) successfully block the hydroxyl group essential for the activity of floxuridine [18].

In order to achieve the goal of aspirin effect without gastrointestinal side effect Fouad et al prepared ASA glutamic acid complex for oral administration [19] and ASA caffeine complex for rectal administration [20]. Also, Anwer et al prepared inclusion complex of ASA in humic acid that significantly reduced ulceration as compared to aspirin alone[21]. Inadequate gastrointestinal bioavailability of many important drug compounds has led the scientists to pay attention toward finding alternative routes for drug administration. Transdermal drug delivery offers several advantages Such as elimination of first pass metabolism, no pain, sustaining drug release, and improves patient compliance especially for long term use [22].

Ammar et al [23,24] prepared aspirin in different topical bases. They found that hydrocarbon gel allowed highest drug release and permeation. Also they found that 5-10% oleic acid and 20% urea provide the greatest enhancing permeation with Carboxymethyl cellulose sodium gel.

The purposes of the present work were to: (1) prepare and investigate the formation of ASA-valine complex, (2) characterize the formed complex using different tools (3) study the release of the complex from different gel bases, (4) study the in-vitro permeation of the complex from different gel bases compared by acetyl salicylic acid alone.

2. Experimental

2.1 Materials

ASA was purchased from E. Merck Company (Darmstadt, Germany) and Valine was obtained from Winlab Ltd. (Leicestershire, UK). Standard cellophane membranes (molecular cut of range = 12000), Pluronic F-127 were purchased from Sigma chemical Company (St. Louis, MO, USA). Sodium carboxymethyl cellulose (Na-CMC) was purchased from wilfrid Smith (Middlesex, UK). Hydroxypropylmethyl cellulose (HPMC) was purchased from (Aldrich Chem. Co., USA). Sodium alginate was purchased from (Judex Laboratories Reagent, UK). Carbopol 934 was purchased from (C.P. Evan Co., England). All other chemicals were either of analytical or reagent-type grade.

2.2. Methods

2.2.1 Preparation of ASA-valine complex by freeze-drying technique

ASA-valine complex was prepared in water, the freeze drying technique was employed. It is a non-sophisticated and commonly used technique with a yield approaching 100% [25,26]. Equimolar (0.01 mole) weights of ASA and valine were accurately weighed. Valine was dissolved in 400 ml distilled water (HPLC grade). Then ASA was added and dissolved in the same vessel. The prepared solution was allowed to freeze overnight at (-20 °C) and then lyophilized over a period of 72 hrs using a freeze-drier (Alpha 1-4 LD-2, Martin Christ, Osterode, Germany) under the following conditions: (temperature= -59 °C, vacuum= 0.090 mbar). The dried powder were then collected and stored at room temperature in a dessicator until further investigations.

2.2.2 Evaluation of the ASA-valine complex

2.2.2.1. Differential scanning calorimetery (DSC)

DSC studies were carried out using differential scanning calorimeter equipped with an intercooler (Shimadzu DSC-60, Shimadzu Corporation, Koyoto, Japan). Indium/zinc standard were used to calibrate the temperature and enthalpy scale. The samples (4-5mg) were hermetically sealed in an aluminum pans and heated at a constant rate of 10 °C/min over a temperature range of 25- 400 °C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

2.2.2.2. Morphology of the prepared crystals

Samples morphology was examined under scanning electron microscope (Jeol, JSM-6360LV Scanning Microscope, Tokyo, Japan). Before microscopy, the dried microparticles were mounted at carbon tape and were sputter-coated using gold (Jeol, JFC-1100 fine coat ion sputter, Tokyo, Japan). The photomicrographies were taken at an acceleration voltage of 15 kV.

2.2.2.3. FTIR spectroscopy and mass spectroscopy

Fourier transform infrared (FTIR) spectrum was recorded on Perkin Elmer FTIR instrument (Perkin Elmer, Waltham, Massachusetts, USA). Samples were prepared as KBr pellet and scanned against a blank KBr pellet background at a wave number ranging from 4000 to 650 cm-1 with resolution of 1.0 cm-1.

2.2.2.4. Nuclear Magnetic Resonance (^1H NMR)

Nuclear Magnetic Resonance (1H NMR) spectra were conducted using a Bruker spectrometer instrument (Bruker Avance 500 MHz Ultrashield NMR, New Jersey, USA). Chemical shifts were 302 given in δ (ppm) relative to TMS as internal standard. The ^1H NMR

spectra for ASA (DMSO-d_6): 2.25 (3H, d, j=5 Hz, $CH_3C=O$), 7.19 (1H, s, C_3-H), 7.36 (1H, d, j=6 Hz, C_5-H), 7.61 (1H, d, j=6 Hz, C_4-H), 7.96 (1H, d, j= 6 Hz, C_6-H), 13.12 (1H, s, COOH), for ASA-valine complex (DMSO-d_6): 2.233(6H, s, C3-$(CH_3)_2$, of valine), 2.49 (3H, s, $CH_3C=O$, of ASA), 3.15 to 3.54(2H, m, C2-H,C3-H of valine), 7.18 (1H, s, C_3-H, aromatic of ASA), 7.36 (1H, d, j=6 Hz, C_5-H, aromatic of ASA), 7.62 (1H, d, j=6 Hz, C_4-H, aromatic of ASA),, 7.917 (1H, m, C_6-H, aromatic of ASA), for valine (DMSO-d_6): 1.02 (6H, m, C3-$(CH_3)_2$), 2.26 (1H,m, C3-H), 3.59 (1H, d, J=5, C2-H).

2.2.2.5. X-ray powder diffraction (X-RPD)

X-ray powder diffraction patterns of ASA, Valine and ASA-valine complex were performed. The samples were irradiated using Cukα radiation with a wavelength of 1.5418 A° at 40 Kv and 40 mA, then analyzed between 2θ angles of 4-60° at a scan rate of 0.06°/ min. Studies of the X- ray powder diffraction of the prepared complex, ASA and valine were conducted using X-ray powder diffractometer (PW1710, Philips, Inc., Netherland).

2.2.3. Preparation of ASA-valine complex in different gel formulations:

All the gel formulations containing 1% w/w ASA-valine complex.

2.2.3.1 Cellulose derivatives and sodium alginate gel bases:

The calculated amount of sodium carboxymethyl cellulose (Na-CMC, 3.5% w/v), hydroxypropylmethyl cellulose (HPMC, 2% w/v) or sodium alginate (Na-alginate,7.5% w/v) was gradually dispersed into the phosphate buffer solution containing the complex (pH 5.5), with gentle stirring using magnetic stirrer until clear transparent viscous solutions and gels were formed.

2.2.3.2 Pluronic F-127 gel bases:

The weighed amount of pluronic F-127 powder, 20% w/v, was slowly added with stirring to cold phosphate buffer containing the complex and left in a refrigerator overnight for complete dissolution of the polymer. A clear transparent gel was obtained when the solutions were left outside the refrigerator at room temperature.

2.2.3.3 Carbopol 934 Gel Bases:

The calculated amount of the polymer,0.5% w/v, was slowly dispersed in phosphate buffer containing complex. The dispersion was slowly stirred using magnetic stirrer, care being taken to avoid the formation of air bubbles. Then the dispersion left overnight at room temperature, to ensure complete swelling. The gel was formed by the addition of trietanolamine (TEA) as neutralizing agent, and the pH was adjusted to 5.5.

2.2.3.4. Viscosity Measurements of the prepared gels:

The viscosity of the investigated ASA–valine complex containing gels was determined using Brookfield DV-III viscometer (Stoughton-MAO2072, USA), at room temperature. Samples were tested using spindle 94 at speed 20 rpm. The reading was taken after a specified time of 1 minute.

2.2.4. In-Vitro release of the ASA-valine complex from the prepared gel formulations:

The in-vitro complex release from gel formulations was studied by dialysis method using cellophane membrane [20] with little modification. One gram of the formulation was placed on a piece of standard cellophane membrane which was pre-soaked in distilled water for 24 hours to remove preservative then soaked with the receptor medium for another 24 hours before its use for

the release study. The loaded membrane was stretched firmly on one of the open ends of a glass tube having a surface area of 3.14 cm^2, using a rubber band. The tube was then immersed in a 250 ml beaker containing 50 ml of phosphate buffer pH 5.5. The temperature was maintained at 37 ± 0.5°C in a thermostatically-controlled water bath shaker (GFL, Germany) with a shaking rate kept at 50 stroke/min.

Samples of 5 ml each from the release medium was withdrawn at suitable time intervals up to six hours and replaced with free buffer kept at the same temperature. The released complex was determined spectrophotometrically at λmax 267 for ASA and 269 for complex using UV spectrophotometer (Shimadzu Corporation, Koyoto, Japan). Each release experiment was performed in triplicate, and the mean readings were used for calculation. The mechanisms of complex released from the prepared gels were analyzed mathematically according to zero order [27], first order [27] and Higuchi diffusion model [28].

2.2.5. In vitro permeation studies of ASA-valine complex through full thickness rat abdominal skin:

The abdominal skin of male albino rats (200–250 g) was carefully shaved with a razor after removal of hair by electric clippers (model 900, TGC, Japan), animals were left for 24 hours to ensure healthy stratum corneum. Animals were sacrificed and parts of 5 cm^2 each (circle of 2.5 cm diameter) of skin on the left and right sides of the abdomen were excised and the skin was thoroughly checked to ensure that no obvious defects were present. The adhering fat and other visceral tissues were removed carefully and then the skin was washed with distilled water and soaked in phosphate buffer pH 5.5 for thirty minutes before use. The skin parts used were 800±50µm of thickness. Rat skin was mounted on the release tube as in the in vitro release, where, the stratum corneum side facing the donor compartment and the dermal side facing the receptor compartment and the same procedure was applied.

The cumulative amounts permeated of drug (µmole/cm^2) from gels were estimated. The flux (µmole.cm^{-2}.hr^{-1}) was computed from the from the slope relationship between the cumulative amount and time. The permeability coefficient Kp was calculated according to Fick's first diffusion law [29] as follows:

$$Kp = J_{ss}/C_d$$

Where: Kp is the permeability coefficient (cm/ h), J_{ss} is the flux (µmole /cm^2/ h), and C_d is the concentration of complex in the donor solution (µmole).

3. Results and discussion

3.1. Differential Scanning Calorimetry

Thermal and spectroscopic methods considered as the main tools in studying and identifying the physical and chemical interactions between drugs, exciepent, polymers or degradation [30-33].

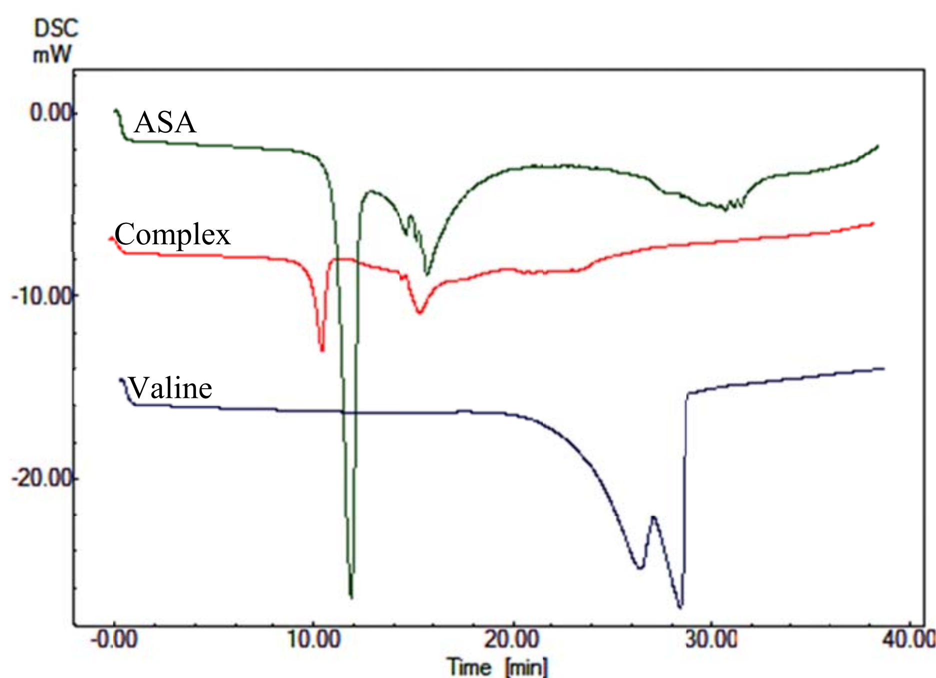


Fig. 2: DSC of ASA, Valine and the formed complex

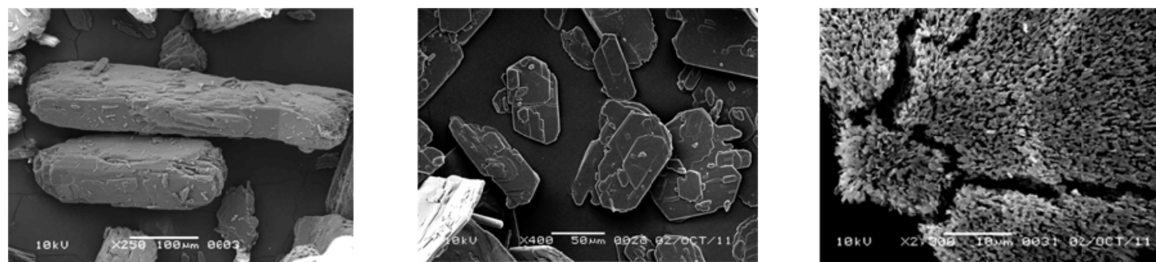
Fig. 2 illustrates the thermal behaviors for each of ASA, valine and their complex. According to Figure 2, and table 1, the thermogram of ASA showed a characteristic sharp endothermic peak at 138.02 °C corresponding to its melting point and ΔH 194.03 J/g. However, the thermogram of valine gives a sharp peak at 299.1 °C, which is corresponding to its melting point and ΔH 101.25 J/g. The thermogram of the formed complex showed an endothermic peak with low melting point at 127.64 °C and lower heat ΔH 33 J/g. Complete disappearance of the two peaks of ASA and valine as depicted in Figure 2 and appearance of new one confirm the formation of the complex. Similar observations were previously reported by Wulff and Alden [34], they concluded that the formation of a complex between indomethacin and ß-cyclodextrin was due to a decrease in ΔH and a lower shift in the peak temperature. So, The present results revealed the formation of complex in 1:1 molar ratio.

Table 1: Peak temperature and enthalpy (ΔH) obtained from DSC thermogram

Parameter	ASA	Valine	Complex
Peak °C	138.02	299.1	127.64
ΔH J/g	-202.08	-101.25	-33

3.2. Scanning Electron Microscopy

Figure 3 shows the scanning electron microscope photographs of the ASA, valine and the resulted complex. The morphological shape of the formed complex crystals showed a clear distinct difference in shape. These crystals of the formed complex are smaller in size if compared to that of ASA or valine, appeared as aggregation of flakes to form a snail like structure with a rough surface. However, ASA crystals were needle shape and that of valine is large hexagonal platy morphology with unequal sides particles.



ASA Valine ASA-Valine Complex

Fig.3: Scanning electron microscope micrographs and surface morphology of ASA, Valine and complex crystals.

3.3. Spectroscopic Studies

3.3.1. FTIR Spectroscopy

The FT-IR technique provides information concerning both the strength of the bonds between atoms and is a useful tool to study the interaction between the organic compounds. Figure 4 showed the IR spectrum of ASA, valine and the prepared complex.

Valine is an amino acid characterized by the presence of amino group and one carboxylic group. On the other hand ASA contains a free carboxylic group. ASA was found to affect the FTIR band of the primary amino group of valine at 3422.1cm^{-1} (stretching band) to a high frequency shift at 3432.51cm^{-1}. Also, it was found the disappearance of the CN band at 1351.31cm^{-1}. As the noticed stretching and bending bands of the quaternary nitrogen bands wave numbers were affected, this may reflect an electron donation from the NH_3^+. With regard to the disappearance of the CN stretching band at 1351.31cm^{-1}, it may be postulated that it was shifted toward a higher frequency combining the band at 1370cm^{-1} giving it higher intensity and reflecting an electron withdrawing effect. At the same time the asymmetric bending of NH3$^+$ at 1611cm^{-1} was also disappeared. The stretching band of the carbonyl group of ester functionality of ASA appeared at 1753 cm^{-1}. Also, the band of the C=O of the ASA carboxylic group appeared at 1690 cm^{-1} and found in the same wavelength in case of the prepared complex. This data may reflect an interaction between the carboxylate and the quaternary nitrogen.

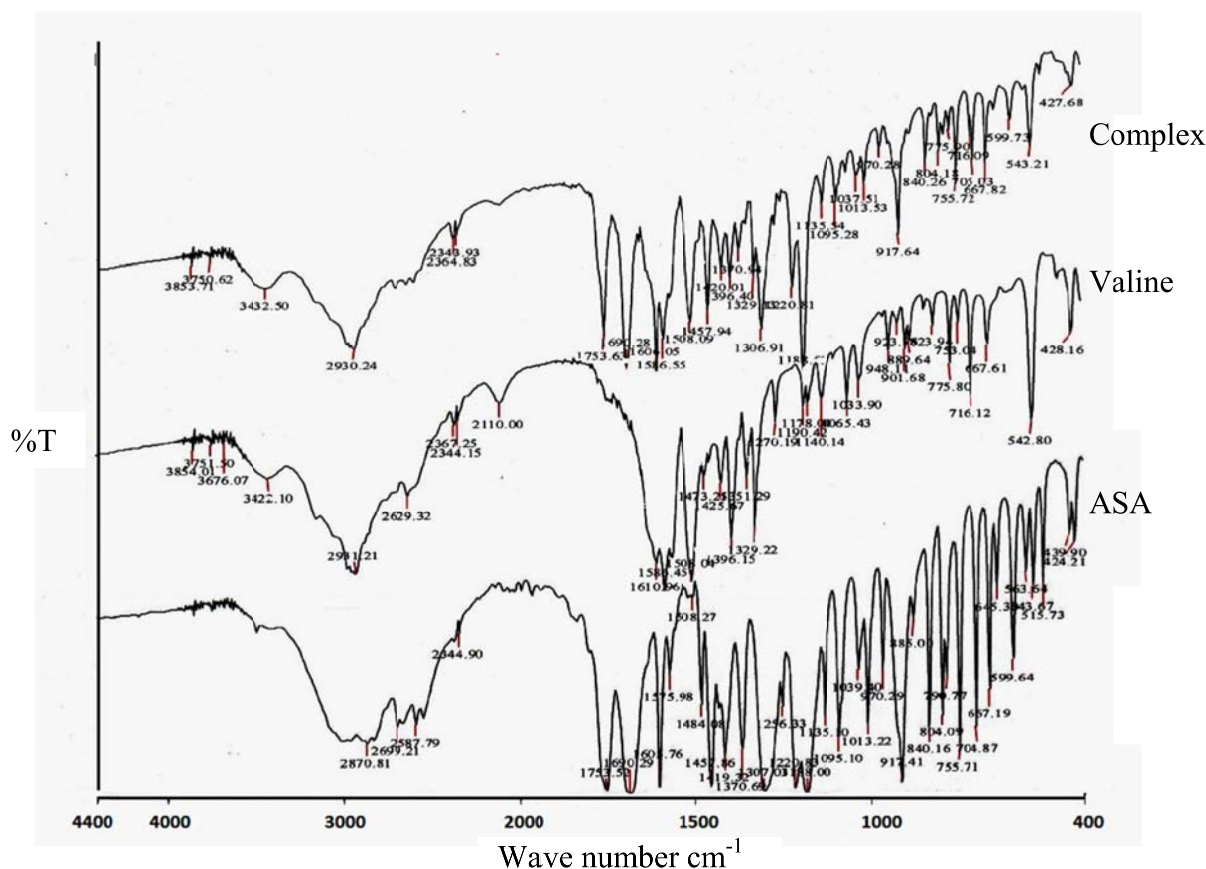


Fig.4: FTIR chart for ASA, Valine and the complex

3.3.2. *^{1}H NMR Spectroscopy*

The ^{1}H NMR results of ASA and the effect of valine on its ^{1}H NMR behavior revealed a great perturbation in coupling and shifting on the peaks. Firstly the carboxylic peak of ASA at 13.12ppm was completely disappeared in the complex. Although there was no effect on the methyl group of the acetyl moiety of ASA peak, there were pronounced downfield shifts in the two methyl groups of valine from 1.02 to 2.023ppm. This downfield shift may be due to an electron withdrawing effect resulting from the formation of NH_3^+. C2H and C3H peaks of valine showed a multiplet at 3.54 having also a down field shift. On the other hand an upfield shift was found in the aromatic C6H by 0.04ppm. These results pointed the presence of an in interaction between ASA and valine to form complex. The given spectral data as well as the DSC data indicated the formation of complex between ASA and valine in 1:1 molar ratio. The most probable description of that complex is that of ionic type involving both the carboxylic group of ASA and the amino function group of valine.

3.3.3. *X-ray powder diffraction (X-RPD)*:

X-ray powder diffraction considered as one of the important tools for studying the crystallographic models (crystal structures), specially when single crystals are not available. Also, it is helpful in determining the presence of different crystalline phases

in a mixture and for studying phase transitions. When monochromatic radiation is used, diffraction intensities are measured as a function of the detector setting angle, 2θ.[35]. The X-RPD patterns of ASA, valine and the prepared complex are shown in figure 5. Valine exhibits a highly strong and characteristic X-RPD pattern, showing the crystalline nature of the powder. L-valine arranged in crystals in monoclinic space groups with alternating hydrophobic (nonpolar chain) and hydrophilic layers (polar carboxylate and amino) parallel to the xy plane. The layer consists of two crystallographically independent molecules A and B with different conformations in the

asymmetric unit. The carboxyl groups of the A and B molecules are coplanar with their respective C_α atoms. The nitrogen atom is surrounded by four oxygen atoms at short distances. [36, 37].

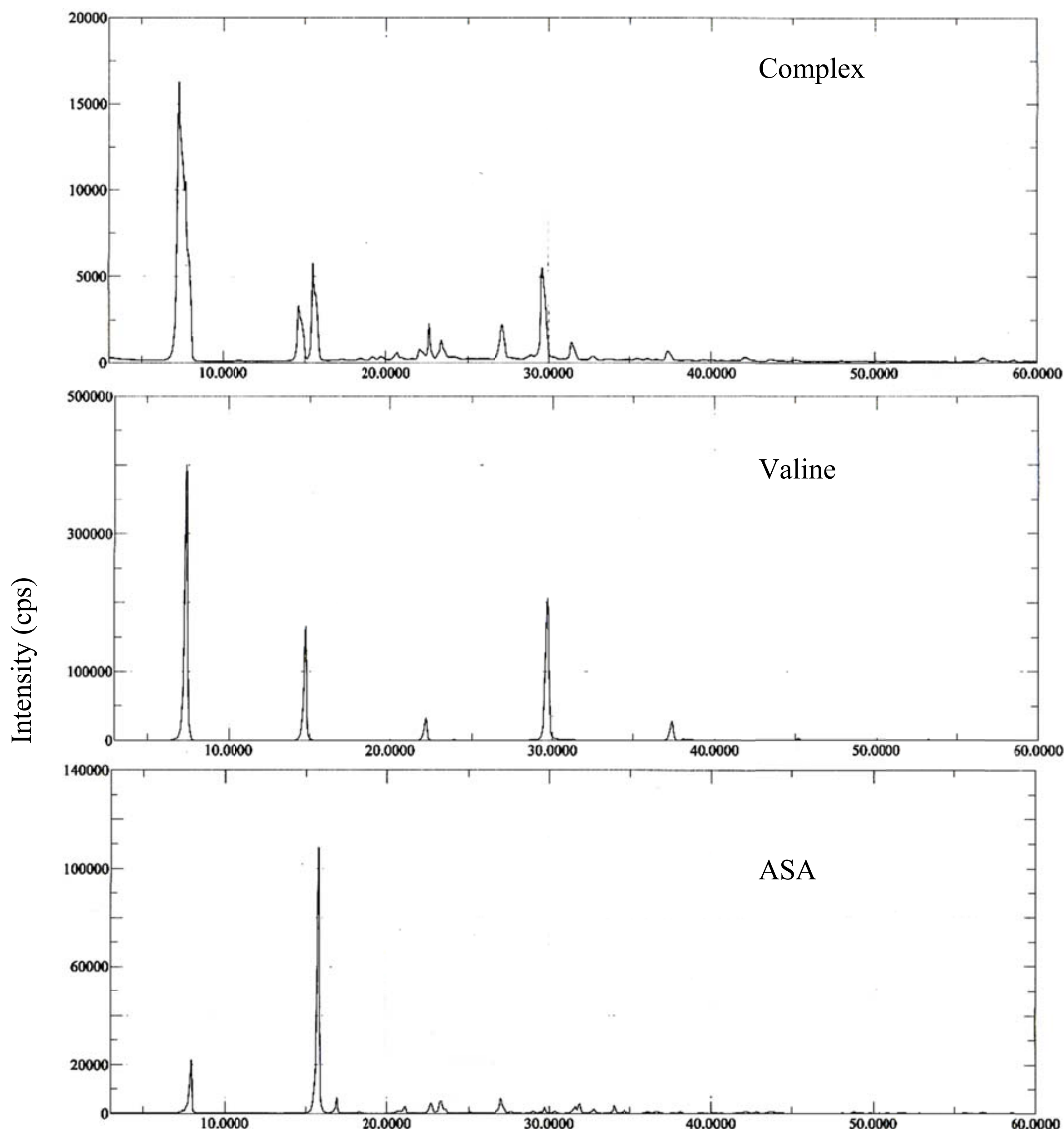


Fig.5 X-Ray Powder Diffraction Patterns of ASA, valine and the complex.

The X-RPD pattern is dominated by the intense scattering peaks located at diffraction angle of 2θ degrees at d-value of 11.904, 5.993, 4.002, 3.004 and 2.405. on the other hand, ASA crystals consists of two dimensional layers stacked along the third dimension the forces of stacking is van der Waals forces, however, within the layers H-bonding is the dominant interaction. It was found that H-bonding interactions have a significant role in the morphology of ASA.

In crystal lattice, ASA molecules are mainly connected in dimers by the familiar carboxylic acid dimeric linkage, involving two symmetry-equivalent H-bonds. [38,39]. ASA was found to exhibit a strong and characteristic X-RPD pattern, showing the crystalline nature of the powder. The pattern is dominated by two intense peaks located at diffraction angle of 2θ degrees at d-value of 11.196 and 5.6273. The X-RPD diffractogram of ASA- valine complex showed scattering peaks located at d-value of 12.1662, 11.5544, 11.1608, 6.0498, 5.9666, 5.7121, 5.6433,

3.281 and 3.014. The peaks of the complex appears with highly reduced intensities and little shifting. This indicate a construction of a new kind of crystals or powder that is of smaller size as noticed in SEM figure 3. These results confirm the formation of complex between ASA and valine.

3.4. *In-Vitro release of the ASA-valine complex from the prepared gel formulations:*

As the complex is a physical complex in 1:1 ratio, each one mole at complete dissociation will give one mole of ASA. All the release calculations were performed in molar concentrations. The prepared ASA-valine complex was formulated in different polymeric gel bases in order to investigate its transdermal application. The influence of the vehicle type on the release profile of ASA-valine complex from the gel formulations was studied. The percentage of complex released from its gel formulations (Na-CMC, HPMC, pluronic F-127, sodium alginate, carbopols 943 neutralized by TEA) up to 6 hours presented in figure 6. The results showed a variation in the release rate of the complex according to the tested gel base, suggesting that the choice of the vehicle is an obvious important for achieving a desired drug release profile. The diffusivity of the drug through any base depends on the composition of the individual base [40]. Sodium alginate gel(7%w/w) exhibited the highest percent of the complex released(99.34%), while 20%w/w pluronic F-127 gel exhibited the lowest release(70.14%) among the tested gels. This may be due to a decrease in the availability of free complex, where, the tendency of the complex to leave the vehicle is strongly dependent on its microstructure [41]. The release pattern of the ASA-valine complex could be ranked as follow: sodium alginate ≥ carbopol 934 ≥ HPMC ≥ Na-CMC ≥ pluronic F-127.

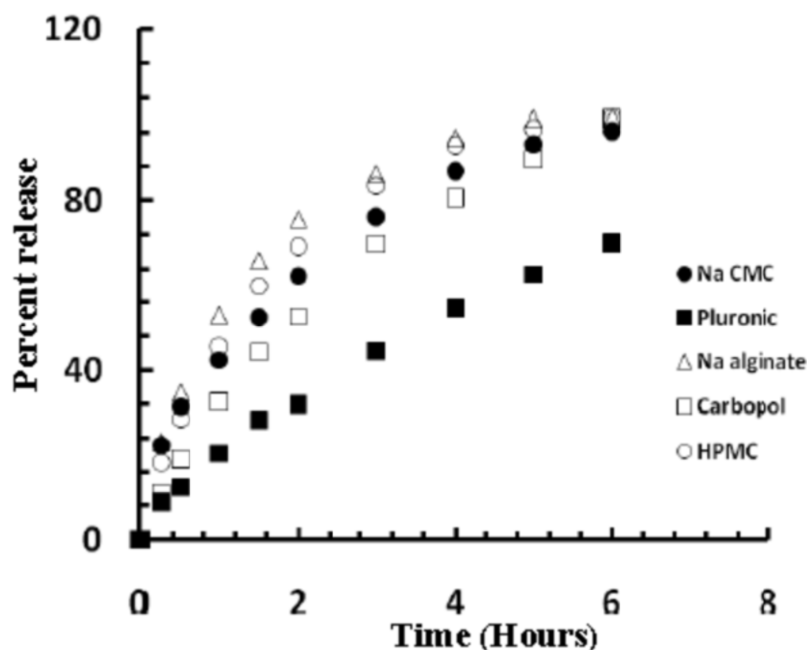


Fig.6: Release of the ASA-valine complex from different gel bases.

The low viscosity of a formulation makes the drug movement more easily than the high viscosity. There was an inverse relation between viscosity of the gel and the released complex; sodium alginate gel has the lowest viscosity (table 3) showed the highest release. Although, the viscosity is most widely utilized parameter for comparison between different gel bases[42], it appears in some cases that the observed differences may be related to other factors such as the differences in the structure of the polymers and/or the presence of drug-polymer interactions[43,44].

Linear regression analysis of the release data fitted according to zero and first-order as well as Higuchi diffusion model to all the *in-vitro* ASA –valine complex release results.

Preference of certain mechanism was based on the correlation coefficient (r) for the parameter involved. Accordingly, the drug release from all gel formulations followed diffusion mechanism.

3.5. In vitro permeation studies of ASA through full thickness rat abdominal skin:

The percentage Cumulative amount permeated of ASA-valine complex from gel formulation is shown in table 2. The extent of percutaneous absorption of a drug appears as a result of many factors. Partitioning of the tested drug between the vehicle and the stratum corneum results in developing a concentration gradient across the skin that is influenced by drug-vehicle-skin interactions [45]. In fact the release of a drug from a topical pharmaceutical preparation can be effectively influenced by the vehicle in which it is applied. A proper formulation of a topical drug will ensure that it exerts its maximal activity on the skin [46]. Table 3 shows the flux (Jss) and permeability coefficient (Kp) of ASA-valine complex in gel formulations through rat skin.

Table 2: Percentage ASA-valine complex permeated through rat skin from different gel bases

Time (hr)	Gel bases					
	HPMC	pluronic	Na alginate	Na-CMC	carbopol	ASA gel*
0.5	7.52	3.61	5.41	8.12	13.83	3.26
1	11.46	10.63	9.7	11.27	19.17	8.05
2	21.57	21.46	21.08	25.33	29.39	24.24
3	29.76	32.99	34.38	40.02	38.86	37.53
4	44.72	43.59	48.48	56.82	53.96	50.63
5	56.67	49.68	59.07	64.37	66.59	61.46
6	76.17	66.21	72.19	70.35	85.57	64.95
12	83.91	72.23	84.14	83.24	96.54	74.02

* ASA in 0.5%w/w carbopol 934 gel

Table 3: In-vitro skin permeation parameters of ASA- valine complex from different gel bases and their viscosity.

Gel base	Jss^a ($\mu mole.cm^{-2}.hr^{-1}$)	Kp^b ($cm.hr^{-1}$)	η^c (poise)
HPMC	5.090	$1.512 X10^{-4}$	43.33
Pluronic	3.915	$1.163 X 10^{-4}$	169.33
Na alginate	4.175	$1.240 X 10^{-4}$	63.67
Na CMC	4.509	$1.339 X 10^{-4}$	106.34
Carbopol	5.321	$1.580 X 10^{-4}$	11.00
ASA gel*	3.910	$1.161 X 10^{-4}$	11.00

* ASA in 0.5%w/w carbopol 934 gel
a; The flux
b; The permeability coefficient
c; The gel viscosity

It was found that ASA-valine complex gel in Carbopol 934 and HPMC showed the highest permeation rate across the hairless rat skin; 5.321 $\mu mole.cm^{-2}.h^{-1}$ and 5.09 $\mu mole.cm^{-2}.h^{-1}$ respectively, followed by Na-CMC, sodium alginate and finally pluronic F-127.

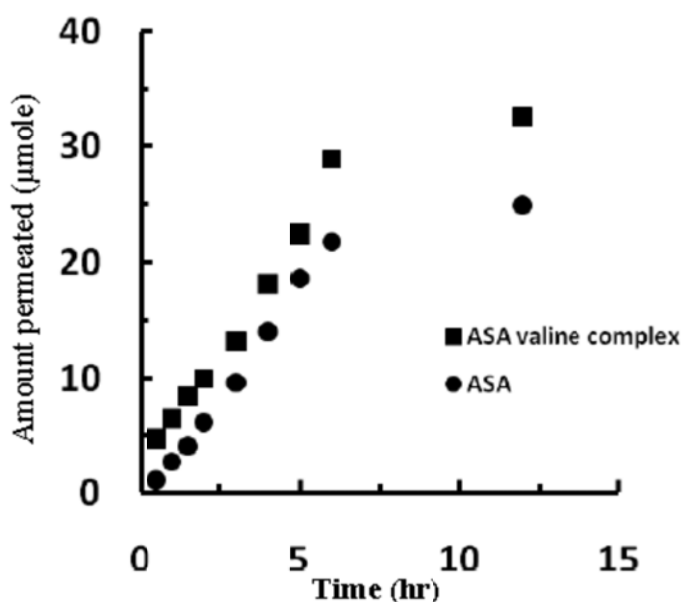


Fig.7 Permeation of the ASA-valine complex and ASA alone each from 0.5%w/w carbopol 934 gel.

As carbopol 934 gel base showed the highest flux for the complex, ASA was formulated in an equimolar (33.67 mmole) concentration to distinguish the difference between ASA and its valine complex as transdermal gel. Figure 7 present the permeation of each of ASA and the valine complex through the rat skin. The results revealed higher flux and permeability coefficient in case of complex than that of ASA alone (5.321 μmole.cm^{-2}.h^{-1}, 1.58x10^{-4} cm.h^{-1} for complex vs 3.91 μmole.cm^{-2}.h^{-1}, 1.161x10^{-4} cm.h^{-1} for ASA. This result certifies that ASA-valine complex has the ability to cross the skin barriers and to permeate through the skin faster than ASA.

4. Conclusions

A cetyl salicylic acid- valine complex has been successfully prepared using freeze-drying method. The complex is of clinical importance as it will replace acetyl salicylic acid in the dosage form and provide a convenient way for transdermal application of acetyl salicylic acid especially those ischemic elderly patients who are using acetyl salicylic acid as an antiplatelet as well as for unconscious patients who are using acetyl salicylic acid as a maintenance therapy.

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