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Contents

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Study of Dysfunction in the Neural Systems in Autism Spectrum Disorders: A Review Article

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ABSTRACT

One of the worst developmental abnormalities, autism spectrum disorder, is often identified before the age of three. All forms of autism impair people's capacity to communicate with others, despite the fact that each person's symptoms and degree of severity vary. Despite the fact that there is no known cure for autism, children who receive prompt and serious treatment see significant improvements in their quality of life. The deficiencies in social functioning seen in individuals with autism spectrum disorders may be brought on by diseases of the neurological systems responsible for processing social information, according to research in the field of social neuroscience. This study examined the available evidence on the neurological underpinnings of autism spectrum disorders. The outcomes demonstrated aberrant activity in sections of the mirror nerve system and its three interrelated regions that are engaged in social perception, areas related to action observation, and regions that are involved in theory of mind. These findings point to faulty social information processing in autism spectrum disorders, which are characterized by flaws in the neurological systems responsible for social perception, action comprehension, and theory of mind. These results emphasize the involvement of the posterior superior temporal sulcus as a common location in all three systems and offer a framework for understanding the brain processes underlying social deficiencies in autism spectrum disorders.

Key words: Neural systems, Autism spectrum disorders, Social neuroscience, Developmental abnormalities

INTRODUCTION

Autism spectrum disorder (ASD), which manifests as inadequate, delayed, or aberrant functioning in one of domains of social interaction, language used in social communication, and creative or symbolic play. A child with autism spectrum disorder lives in his inner world, and since establishing appropriate social communication requires receiving and processing sensory information correctly and adopting appropriate behavior based on this information, his connection with the outside world is cut off, and the lack of receiving and understanding external sensory stimuli disrupts his learning process and appropriate social communication [1,2].

Cognitive neuroscience has begun the study of neural structures and circuits underlying the processing of social information and the social brain in humans. Particularly, the discipline of social neuroscience is expanding quickly, and its primary study subfields have aided in describing the distinct elements of both healthy and disordered social information processing [3,4]. Therefore, it seems necessary to describe the abnormal performance of the key systems of social information processing in autism spectrum disorders by reviewing the research that has examined the neural mechanisms of these systems.

The neural system of social perception

People are naturally sociable beings. Due to its efficiency and reflective character, social perception skill is

is described as the capacity to interpret the mental states of others based on fundamental behavioral cues [3,5]. This capacity is thought to be evolutionary advantageous. Numerous efficient and explicit mechanisms that develop later in the course of transformation require social awareness to function [6]. Research on primates is seen as a helpful model for understanding social perception in humans since similar social behaviors have been seen in monkeys [7,8]. For instance, chimpanzees are able to comprehend what their peers are aware of in the context of competition for food. They can assist their fellow humans by using their knowledge of others' motivations [9,10]. According to research, Rhesus monkeys may estimate what other people are thinking based on what they hear and observe [11,12]. The fusiform gyrus (FFG), amygdala (AMY), orbitofrontal cortex (OFC), and posterior superior temporal sulcus (PSTS) all need to be active for dynamic social perception. In both humans and monkeys, these regions are selectively responsive to social cues and are linked in the primate brain [13,14].

In the network of social perception, PSTS is crucial. This region is directly connected to the major visual and auditory centers in both monkeys and humans, and it participates in the representation of information in both areas [15,16]. PSTS selectively activates against static social stimuli (such as faces) and dynamic and complex social information (such as changes in gaze direction or facial emotions) [16,17]. PSTS is sensitive to social stimuli that people interpret as deliberate [16] and is activated against static social stimuli (such as faces).

In comparison to non-target acts, PSTS exhibits more discriminating behavior toward intentional human behaviors that have social significance. The processing of emotional speech via PSTS is crucial in the auditory domain.

The FFG is comprised of a number of different but connected areas that are engaged in the visual facets of social perception along the ventral-temporal cortex. They include the fusiform face area (FFA), which responds to facial cues, and the fusiform body area (FBA), which only responds to physical stimuli. The FFA is sensitive to distinct fixation patterns and simple eye movements during implicit face processing [18]. In addition, FFA in facial identity recognition and goal-directed actions is involved [19]. AMY encodes the emotional significance of social information, especially when such information requires rapid and reflexive processing [20]. For example, the amygdala enhances gaze orientation toward facial features that contain socially relevant information, such as eyes, especially when facial expressions are associated with fear [21]. The OFC is related to the reward encoding of environmental sensory cues, which is a fundamental aspect of behavioral planning in humans as well as in primates [22]. Paying attention to socially rewarding stimuli, determining personal interest in social interactions, and responding to social cues [23] requires the activity of this area due to its central role in value-based decisionmaking.

Our knowledge of the social development and social deficiencies of people with autism spectrum disorders has been improved by studies that look at social perception in these diseases. Compared to normal children, children with autism spectrum disorders pay less attention to social cues such as voices and faces [24]. Children with autism spectrum disorders tend to place more emphasis on physical and non-social relationships than their typical classmates do at this age, failing to recognize the social significance of biological functions [25].

Social difficulties seen in autistic spectrum diseases in young children continue throughout adulthood. Autistic adults with high activity have difficulty inferring the mental states of others, vocalization, and emotional facial expressions [26]. According to these results, there is compelling evidence of aberrant cortical and subcortical social perception processing for somatosensory, auditory, and visual inputs. The AMY FFC and PSTS brain regions, which are involved in social perception, are less active in autistic children than in their non-autistic siblings when they are seen making displays or motions, according to studies in the domain of visual signals [27]. In particular, it appears that autism spectrum disorders show

less selective PSTS area performance in social perception. Compared to normal people, the function of this area in people with autism spectrum disorders is less specific to evaluate the inconsistency of the actions of the characters in a show with their displayed preferences at the beginning. In the auditory domain, those with autism spectrum disorders have the same pattern of activity as the control group for non-vocal sounds, but the sound selection regions in PSTS become inactive in response to vocal sounds. In terms of somatosensory signals, individuals with high levels of autism features had decreased activity in the OFC and PSTS regions in response to a light touch of the arm [28,29].

The nervous system of action observation

While social perception is concerned with comprehending and interpreting the outward behaviors of others in order to infer their underlying intentions, the function of the perceiver is not entirely obvious. Another process that significantly depends on the perceiver himself is active when individuals react to the behaviors of others. An individual who is observing the behaviors of others may be attempting to comprehend what such actions would entail if he were to carry them out himself. Therefore, the role of a self-perceiver is important, and understanding the actions of others is to some extent self-based. This is the mechanism of the nervous system of perception or action observation. Perceivers must go beyond simple decoding in order to correctly match their behaviors with those that are being watched [30]. The perceiver must first see another person's activity in order to grasp it, and only then can they mentally mimic it. As a result, imitation and action perception are strongly connected. Mirror neurons, a subclass of visuomotor neurons first identified in the prefrontal cortex of monkeys, have received the majority of attention in studies investigating the neurological basis of action perception and observation. Mirror neurons have been identified in humans and monkeys in response to action observation and execution. Three interconnected brain regions make up the mirror nerve system in humans [31,32]: the parietal mirror neuron region, which contains the front section of the inferior parietal lobule (IPL) and offers low-level motor description of other people's movements; the PSTS area, which serves as an intra-visual area of the dynamics of other people's actions; High-level motor plans are created in the frontal mirror neuron area, which comprises the ventral premotor cortex (PMC) and posterior inferior frontal gyrus (IFG). The process of action perception in the mirror nervous system is a crossroads process [31].

The IPL and the IFG receive the data encrypted in the PSTS. The data is subsequently sent via the IFG to the IPL and PSTS. As a result, PSTS functions as both an input and an output area in the mirror nervous system, enabling comparison between seen activities and those that have been carried out. The study of action observation is still relatively new but is expanding quickly. While some studies have found that autistic children perform poorly in imitation activities or exhibit delayed development when compared to their typical counterparts, the question of whether there is a problem in the imitation process in autism is still up for dispute [33]. Other studies have reported the same performance in the field of imitation both in autistic children and in the control group [34, 35].

The mirror neuron system in autism disorder has been the subject of several neuroimaging investigations, with varying degrees of success. On the one hand, the outcomes of functional magnetic resonance imaging (MRI) studies suggest that kids with autism spectrum disorders display aberrant activity in particular areas of the mirror nerve system, such as TFG and IPL, when watching facial expressions or hand motions [36]. According to the electroencephalography (EEG) results, mu rhythm attenuation is typically observed in people going through normal neurodevelopment during observation and execution of hand movements. People with autism spectrum disorders do not exhibit mu rhythm suppression when watching an action. The neural activity of regions of the brain related to the mirror nervous system in persons with autism spectrum disorders and those in the control group, on the other hand, has not been observed to vary in other investigations [37,38]. It is interesting to note that research

showing aberrant neural activity of the mirror nervous system typically employ emotional stimuli, whereas studies showing normal activity of the mirror nervous system typically utilize non-emotional stimuli [39]. There is a developing tendency in the research of the mirror nervous system, and work is still being done to rectify the way that the distinct roles played by the mirror nervous system's various brain regions are recognized.

Theory of mind and malfunction of neural systems

In the last two decades, theory of mind (also known as mentalizing or mental state reasoning) research has shed light on both typical and pathological social behavior. The capacity to anticipate connections between the internal states of the mind and the exterior conditions of circumstances is referred to as the theory of mind. To be able to do this, one must be able to distinguish their own reality from what others see [40]. Contrary to what is seen by others and what may be observed in the act of reasoning about mental states, it is thought to be a human-only ability that calls for significant cognitive resources and high levels of attention. People can successfully navigate the challenging social environment if they have the capacity to comprehend and forecast the mental states of others [41].

Wimmer and Perner conducted the famous Sally-Anne experiment on young toddlers in 1983 to test the theory of mind [42]. Children watch Sally and Anne, two dolls, as part of this exam. After placing the stone in her basket, Sally exits the room. She removes the stone from Sally's basket and places it in her box while she is not there. Participants in this test are required to respond to the following question : Where will Sally seek her stone when she enters the space again ? The children will answer that Sally will seek the rock in the basket that she placed it in if they are able to appreciate Sally's perspective, or, to put it another way, if they comprehend that Sally has a mistaken notion about the position of the rock. The clear grasp of another person's incorrect belief is a developmental milestone that children acquire around the age of four, according to developmental psychology experts who have used this test or variants of it. The second-level false belief tests are successfully completed by typical youngsters between the ages of 6-7 [43]. The development of more sophisticated mental-state reasoning, including moral judgment, occurs between puberty and maturity.

According to research, those who suffer from autism spectrum disorders exhibit deficiencies in their theory of mind. Even though they were approximately five years older than the other test subjects, children with autism spectrum disorders who completed Sally's task could not recognize Sally's incorrect notion [44]. According to the results of various studies that have compared mentalization skills in normal and abnormal children, failure to recognize false beliefs is considered a sign of more fundamental social deficiencies in autism spectrum disorders [45, 46]. Although those people with autism spectrum disorders who have medium or medium to high IQ learn to solve simple false belief tasks during the transformation, their performance in more advanced tests that are combined with complex social emotions and natural feelings shows that their shortcomings in the field of inferring mental states are stable in adulthood. Adults with high-functioning autism can understand false beliefs when tested, but they are not able to spontaneously predict false beliefs based on behavior [47]. An increase in knowledge about inferences about the mental states of both persons with these illnesses and healthy individuals has resulted from extensive study on the theory of mind in autism spectrum disorders utilizing a range of activities. Numerous neuroimaging studies have concentrated on the deficiencies in theory of mind in people with autism spectrum disorders. Studies that have investigated mentalization using static tasks have concluded that MPFC and TPI activity in people with autism spectrum disorders show a decrease compared to normal people, and the more severe the symptoms of these disorders are, the greater the decrease in the activity of these areas [48]. However, in another study, no difference was found between the neural activities during the story-oriented theory of mind task in these subjects

in the control group [49].

Overall, a vast number of recent studies suggest that individuals with autism spectrum disorders have atypical spatial activity patterns and lower activity of the fundamental mentalization regions, including TPJ and MPFC, while assuming the mental states of others.

CONCLUSION

The posterior superior temporal sulcus AMY, orbitofrontal cortex, and fusiform gyrus are among the brain regions involved in social perception. The results of studies that looked at the neural mechanisms of social information processing in the brains of people with autism spectrum disorders suggest that these individuals are in these regions as well. They exhibit decreased activity in the regions involved in action observation, such as the mirror nervous system and its three interconnected regions, the posterior cingulate cortex/pericaneus, inferior frontal gyrus, and inferior parietal lobule, as well as in the regions dedicated to theory of mind, such as the middle prefrontal cortex, temporal-parietal junction, PSTS, posterior cingulate cortex/pericaneus, and anterior temporal lobe. As a hub connecting these three systems, PSTS is particularly significant and plays a crucial part in the temporal integration of indicators of others' behavior from the senses of sight, sound, and touch, as well as intentional representation [50].

The capacity to create and integrate information throughout time into a cohesive whole in order to comprehend and predict when events will occur is known as temporal integration. This area must be active in order to forecast the temporal encoding of others' conduct [51], and improper activity in ASD makes it difficult to predict others' future behavior based on their past behavior, which is consistent with the recently proposed theory of poor temporal prediction in ASD [52]. Predictive impairment in autism (PIA) is a theory that claims ASD is linked to an erroneous state-by-state conditional probability estimate for an observed temporal sequence. The PIA hypothesis is significant because it offers a framework for comprehending some characteristics of ASD, such as sensory abnormalities, a preference for monotony, difficulties interacting with dynamic objects, difficulties with the theory of mind, and an aptitude for strictly rule-based disciplines like math, music, and computers. In light of this, it is intriguing to speculate that PSTS plays a role in the temporal integration of the essential components of the dynamic stimulus environment, particularly the integration of the visual and auditory systems. Future research should therefore focus on further examining PSTS's temporal integration and how it relates to the PIA hypothesis.

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Clinical Evaluation and Standardization of Image Quality and Technical Protocols for Special Radiological Procedures

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ABSTRACT

This work aimed to standardize and state" the insufficiencies outlined and variation in image quality, among some hospitals in Sudan for a common in specific radiologic examinations. A subjective evaluation of 1,103 image reproductions from "363 special radiologic procedures including Intravenous Urography (IVU), Hysterosalpingography (HSG), GIT barium studies" and Micturating Cystourethrography (MCUG), and theEntrance Air Surface Kerma (ESAK) values recorded for each procedure. The maximum scores ranged as Fully Acceptable; all anatomical structures were found to be i65.9 ±14.9, i53.2 ±21.4, i61.6 ±13.7, 53.2 ±28.86, 62.5 ±15.53 and 64.9 ±18.92 for IVU, voiding Cystourethrography, (barium swallow), (barium meal + barium followthrough), (barium enema) and HSG, respectively. In addition, the ESAK values recorded in this hospital survey were 1.9 ± 0.89, 1.85 ±0.48, 2.3 ± 0.85, and 2.1 ± 0.59 mGy for IVU, Voiding Cystourethrography, "Barium studies and HSG", respectively. The image criteria scoring systems (ICs) were found to be valuable and proposed to endorse in daily practice in the hospitals, and coupled the radiation dose to the patient to the required image quality. This study will help to standardize the image quality of some special examinations typically used in hospitals in Sudan.

Key words: Image quality, Radiographic special investigations, Barium studies, IVU

INTRODUCTION

The diagnostic image is a depiction of the structures of the organs and tissues that are investigated [1]. Image quality determines how effective the image is for its intended task [2-4]. Few reported studies have considered the evaluation of radiographic technique and the diagnostic requirements and radiation dose criteria, either in Sudan or worldwide. In most hospitals, a lack of standardization reduces diagnostic efficiency [5]. To guarantee a standard of quality, the Commission of European Communities (CEC) has endorsed image quality criteria, which are applied globally to ensure good radiographic practices and efficient image assessment [6, 7]. This made the imaging process more efficient in many clinical settings [8].

In this study, we attempted to implement standards in multiple Sudanese hospitals to improve diagnostic efficiency and fully comply with CEC guidelines. This study aims to analyze the quality of the images taken during special radiological procedures, comparing the findings with global standards to see whether these measures allow for reasonable image quality assessment.

MATERIALS AND METHODS

This observational, retrospective study was carried out in nine major hospitals in Khartoum, Sudan. Data from ten x-ray units were used in the study. A subjective evaluation was done on 1,103 images of fluoroscopic investigations, including intravenous urography (IVU), Hysterosalpingography (HSG), GIT barium studies, and avoiding Cystourethrography (MCUG).

Study population

A number of 363 special fluoroscopic investigations were examined, retrospectively: 26.2% (95 patients) were barium procedures, 12.9% (47 patients) were MCU procedures, 27.3% (99 patients) were IVU procedures and 33.6% (122 patients) were HSG procedures. For each procedure, the mean values of patient age (years), patient weight (kg), tube potential (KVp), and exposure settings (mAs) were recorded. More details are provided in Table 1.

Table 1. Number of exams, number of radiographs, and mean values for patient demographic information (height, age, BMI, and weight)

Exam	No.	Patient age (yrs.)	Height (cm)	Weight (kg)	BMI (kg im^{-2})
VU	99	24–45	151.5 (145–158)	59.5 (51–68)	24.9 (22.7–27.2)
MCUG	47	18–67	148.5 (135–162)	57.5 (40–75)	26.3. (21.9–28.6)
Barium studies	95	16–80	145 (125–165)	57.5 (37–78)	27.3 (23.7–28.7)
HSG	122	27–41	165.0 (156–174)	66.5 (51–82)	24.4 (21.0–27.1)

Intravenous urography (IVU), barium studies, voiding Cystourethrography (MCUG), Hysterosalpingography (HSG)

The number of Images (percentage%) of UV, MCUG, barium studies, HSG were 354 (29.9%), 163 (13.8%), 239 (27%), 347 (29.3%), respectively. The total Number of images was 1103.

Image quality analysis

The analysis of Image quality depends on two criteria namely, clinical and procedural and technical criteria. A list of criteria used for image analysis, which comply with CEC guidelines, is illustrated in the following (Table 2).

The term percentage differences (PDs) is used in this discussion to express the differences between the means of the technical quality criteria (TQC) and procedural quality criteria (PQC) as minimum hospital percentage and maximum hospital percentage value.

Table 2. IVU, MCUG, barium studies, and HSG image criteria and respective codes

	No.	Criteria	Code
IVU	**1**	1. Visualization of the whole urinary tract, from the upper pole of the kidney to the base of the bladder.	**C1a**
	2	2. Visualization of the kidney outlines.	**C2a**
	3	3. Visualization of the renal pelvis, the calyces (Pyelographic effect), and the pelvic-ureteric junction.	**C3a**
	4	4. Visualization of the area normally traversed by the ureters and the entire bladder.	**C4a**
MCUG	**1**	1. Visualization of the whole urinary bladder area to the base of the urethra.	**C1b**
	2	2. Visualization of the urethra.	**C2b**
	3	3. Visualization of the vesicoureteral junction.	**C3b**
	4	4. Visualization of the area normally traversed by the ureters and the whole bladder area.	**C4b**
BARIUM STUDIES	**1**	1. The bowel pattern is visible with minimal blurriness.	**C1c**
	2	**1.** Coverage of the whole abdomen, including the esophagus and diaphragm, down to the symphysis pubis.	**C2c**
	3	2. Sharp image of the bones and the interface between the air-filled bowel and the surrounding soft tissues with no overlying artifacts (e.g., clothing).	**C3c**

	4	3. Good tissue differentiation in the visualization of the esophagus, small intestine, large intestine, stomach, or the GIT accessory organs.	**C4c**
HSG	**1**	**2.** Visualization of the uterus opacification or uterine outline.	**C1d**
	2	Visualization of the fallopian tubes.	**C2d**
	3	**3.** Visualization of the Fimbrial rugae.	**C3d**
	4	**4.** Visualization of intraperitoneal spillage.	**C4d**
IQS	**C1**	Weakly visualized and not diagnostic.	Yes/No
	C2	Weakly visualized but diagnostic.	Yes/No
	C3	Good visualization and diagnostic.	Yes/No
	C4	Outstanding visualization.	Yes/No

Intravenous urography (IVU), barium studies, voiding cystourethrography (MCUG), Hysterosalpingography (HSG), and image quality scores (IQS).

Quantitative evaluation method

First, the skin dose (ESD) is calculated based on the x-ray tube output parameters. For patients who underwent fluoroscopic imaging, the following parameters were recorded to estimate the ESD: peak tube voltage (Kvp), a current-time product of exposure (mAs), and focus-to-film distance (FFD). The ESD of the fluoroscopic investigation was quantified directly by calculating the entrance air surface kerma (ESAK) for the patients who underwent IVU, MCUG, a barium study, or HSG, as shown in the following formula [9]:

$$ESAK = op \times \left\{ i \frac{kv}{80i} \right\}^{2} \times mAs \times \left\{ \frac{i100}{FSD} \right\}^{i2} BSF \quad (1)$$

Where op is the output in mGy/mAs at a distance of 100 cm from the x-ray source laterally, Kv is the peak tube voltage recorded for any particular exam; mAs is the current time product, and FSD is the focus-to-skin distance (in cm).

BSF is the backscatter factor, calculated automatically by the Dose Cal software after all input data is entered manually.

RESULTS AND DISCUSSION

The fluoroscopic examination images were subjectively categorized as Fully Acceptable (minimal or no defects), Partially Acceptable (major defects but sufficient clinical information), or Poor (major defects and inadequate clinical information). There were 478 images collected from male patients and 625 images collected from female patients. The Number of IVU, MCUG, Barium studies, HSG in male patients were 212, 131, 135, 0, respectively. The Number of IVU, MCUG, Barium studies, HSG in female patients were 142, 32, 104, 347, respectively. The mean, standard deviation, minimum, and maximum of films per exam for all investigations are shown in Table 3.

Table 3. The mean, standard deviation, minimum, and maximum of films per exam for all investigations

No.	Exams	Mean	Std. Deviation	Minimum	Maximum
1	**IVU**	6.7	2.95	4.00	19.00
2	**MCUG**	9.5	7.63	3.00	34.00
3	**B. swallow**	14.6	12.59	2.00	55.00
4	**B. meal**	19.9	10.43	6.00	41.00
5	**B. follow-through**	12.9	7.91	3.00	28.00
6	**B. enema**	12.4	5.87	4.00	25.00
7	**HSG**	5.8	4.18	2.00	22.00

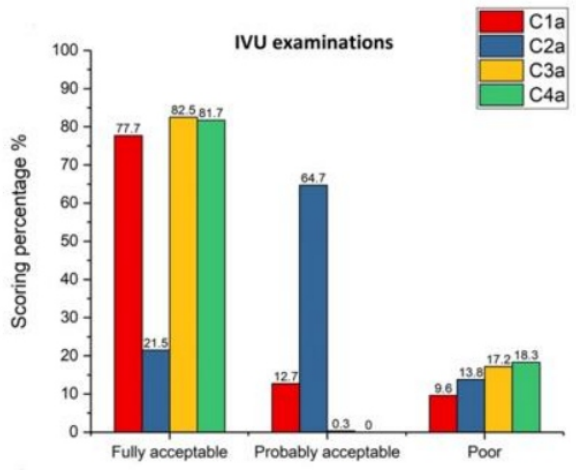
Intravenous urography (IVU), barium swallow (B. swallow), barium meal (B. meal), barium follow-through (B. follow-through), barium enema (B. enema), voiding Cystourethrography (MCUG), Hysterosalpingography (HSG).

The mean number of images per exam, the minimum values, and the maximum values were recorded in (Table 4). Comparable values of the maximum image quality score have been recorded for the examined radiological procedures (Table 4).

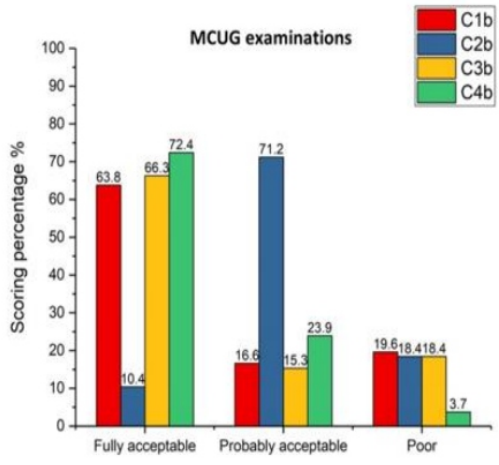
Table 4. Measurements recorded for the maximum image quality scores

Exams	IVU	MCUG	B. swallow	B. meal + if-through	B. enema	HSG
No. of measurements	275	104	105	70	66	277
Maximum image quality scores	65.9 ±14.90	53.2 ±21.37	61.6 ±13.66	53.2 ±28.86	62.5 ±15.53	64.9 ±18.92

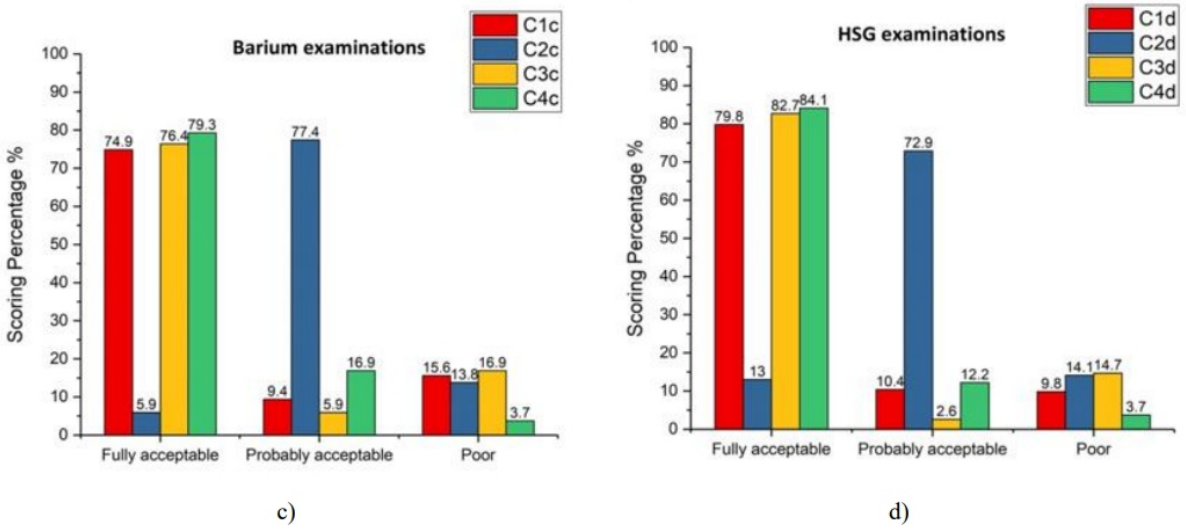
Intravenous urography (IVU), barium swallow (B. swallow), barium meal (B. meal), barium follow-through (B. if-through), barium enema (B. enema), and Hysterosalpingography (HSG).



a)



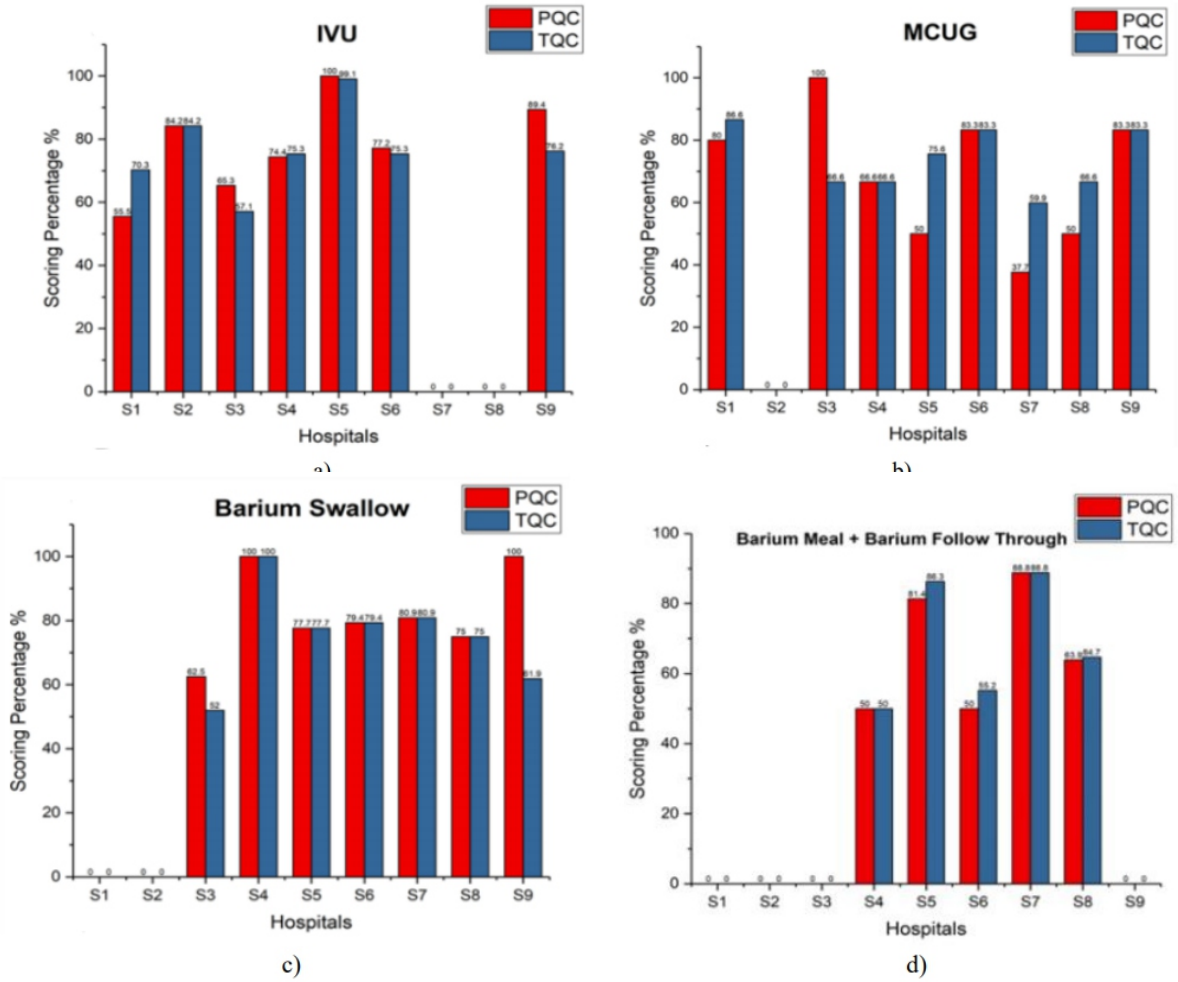
b)



c) d)

Figure 1. Image criteria and codes across all included exams.

The maximum image quality criteria scoring percentage values of technical quality criteria (TQC) and procedural quality criteria (PQC) for all procedures is summarized in Figure 2.



a) b)

c) d)

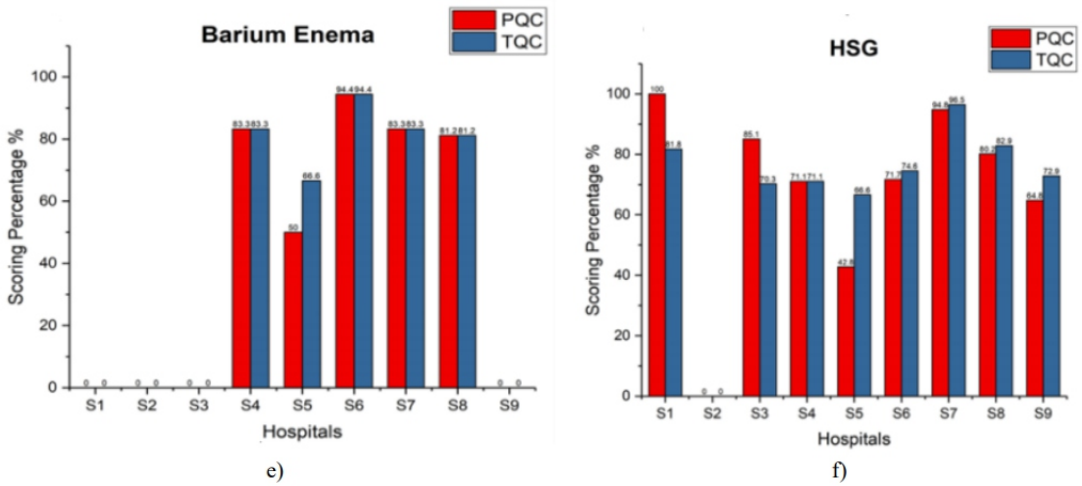


Figure 2. The maximum image quality criteria scoring percentage values of technical quality criteria (TQC) and procedural quality criteria (PQC) for all procedures for each hospital.

The range values for ESAK consisted of x-ray tube potential, focus to film distance (FFD), patient size, filtration applied, and automatic exposure control (AEC), as seen in Table 5.

Table 5. Special investigations with mean KVp, mAs, and ESAK doses to patients at different hospitals

Examination	*KVp*~ Range	*MAs*~ Range	FFD	Mean ESAK mGy
IVU	60–86	10–50	100/109	1.9 ±0.89
MCUG	55–90	8–46	100/109	1.85 ±0.48
Barium studies*	60–125	3–43	100/109	2.3 ±0.85
HSG	63–85	10–40	100/109	2.1 ±0.59

*Barium studies = B. meal, B. follow-through, and B. enema

The clinical evaluations used in this survey were subjective. Error reduced by using suitably skilled groups of radiologic technologists and gathering a huge set of data. This evaluation of the image quality of IVU, MCUG, barium studies, and HSG films in Sudanese hospitals was done using standard techniques and low ESAK values. As illustrated in Figure 1, the maximum image criteria scores range from 53.2 % to i65.9 %, and specific maximum image quality scores were 65.9 ± 14.90 for IVU, 53.2 ± 21.37 for MCUG, 61.6 ± 13.66 for barium swallow, 53.2 ± 28.86 for barium meal and follow-through, 62.5 ±15.53 for barium enema, and 64.9 ± 18.92 for HSG, in compliance with CEC recommendations. The ESAK values documented in this hospital survey were 1.9 ± 0.89, 1.85 ± 0.48, 2.3 ± 0.85, and 2.1 ± 0.59 mGy for IVU, MCUG, barium studies, and HSG, respectively. The obtained values are consistent with each other and with the data presented in the scientific and medical literature [10-14].

The Percentage difference (PDs) of IVU, MCUG, barium swallow, barium meal, barium follow-through, barium enema, and HSG were found to be 15.29%, 4.79%, 24.73%, 10.74%, and 9.89%, respectively. This suggests that the PQC depends on the radiographer's technique to indicate more diverse values than the TQC. The causes of poor image quality are normally technical; for example, exposure factors (KVp, mAs, and type of filter) and other procedural/equipment considerations.

The maximum image quality scores yielded 62.9, 84.2, 61.2, 74.8, 99.5, 73.6, and 82.8. The mean ESAK per IVU procedure was 1.1 mGy, 2.1 mGy, 3.6 mGy, 1.0 mGy, 1.6 mGy, 1.6 mGy, and 2.4 mGy in S1, S2, S3, S4, S5, S6, and S9, respectively. The average means were 77 ±13.27 and 1.9 ±0.89 mGy for IQC and

ESAK, respectively.

The CEC guidelines recommend 10 mGy as a reference dose for an IVU; this means that the patient dosimetry values observed in this work are well within the recommended dosage recognized worldwide. These variations may be explained by the comparatively small numbers of IVU images in the current survey range (approximately 6.4), or perhaps equipment performance improved due to developments in imaging technology. The ESAK values observed here were similar to those found by Halato et al. (2010), in a study conducted on adult patients [14]. The dose value in our work was less than what was stated to be as dose for adult patients in the study by Suliman et al. (2014) [15]. The quality criteria applied, generally, include a system for assessing other general aspects of the image, such as blackening, contrast, sharpness, and diagnostic acceptability. The maximum image scores were 61.6 ±13.66 for barium swallow, 53.2 ±28.86 for barium meal and follow-through, and 62.5 ±15.53 for barium enema. The highest ESAK value for barium studies (3 mGy) was recorded at Hospital 3 (S3), while the lowest ESAK value (1.4 mGy) was recorded at Hospital 6 (S6), with a mean average of 2.3 ± i0.85. Sulieman et al. (2010) quantified the patients' radiation doses during barium examinations [16].

The mean ESAK value was found to be 2.1 mGy per image for HSG, which is close to the range reported in the literature [17, 18], while the number of images for this study was five per fluoroscopic investigation. However, we also found that in two private hospitals, up to 22 images were recorded in some radiographic exams where HSG investigations were. The image quality criteria scoring system is eligible to facilitate the practice in any diagnostic department with no need for a special instrument or dose assessment. However, the IQS will only benefit a radiology department if the staff is willing to identify and correct the shortcomings in their radiographic technique.

CONCLUSION

The results obtained in this work, demonstrate that the analysis of medical image quality is important for assessing the medical imaging process in a clinical setting. The image quality depends on multiple factors, including personnel training, protocols, and equipment type and output. These factors, together with a lack of worldwide standards, mean that both image quality and dose parameters vary from hospital to hospital. This may increase the risk of irradiation in patients undergoing specific fluoroscopic imaging.

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CONFLICT OF INTEREST :

None

FINANCIAL SUPPORT :

None

ETHICS STATEMENT :

This study was approved from Hail University and Health sector in Khartoum and written informed consents were gotten from all patients

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Enhancing the Dissolution of Oral Dasatinib Tablets Using Zein–Hydroxypropyl Methylcellulose Solid Dispersions

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ABSTRACT

Zein has been used in several pharmaceutical applications because of its unique composition. It is an amphiphilic molecule that is biodegradable, biocompatible, and has adhesive, matrix-forming, and film-coating properties, making it a promising pharmaceutical excipient. Zein-based formulations have been investigated in tablet coating, nanoparticulate delivery systems, and controlled-release formulations. However, to date, very few studies have been performed on the inclusion of zein in solid dispersion formulations to enhance drug dissolution. This study aimed to improve the dissolution of the weakly basic and poorly soluble oral dasatinib (used as a model) using zein–hydroxypropyl methylcellulose (HPMC) solid dispersion to achieve rapid disintegration and dissolution in the gastric pH. Using the spray-drying technique, four solid dispersions were prepared with different zein, HPMC, and dasatinib ratios. Subsequently, five different tablets were directly compressed using the previously prepared solid dispersions along with basic excipients. Various in vitro characterization analyses were performed to predict their behavior in vivo. Particle size measurement, tablet weight variation and content assay, disintegration, and dissolution studies were also performed. The results indicated that zein solid dispersion improved the disintegration and dissolution of dasatinib in the gastric media by reducing the drug particle size and the formation of the dasatinib amorphous state. Moreover, the tablets exhibited desirable properties in terms of high drug content, friability, and tensile strength. In conclusion, tablets comprising zein–HPMC solid dispersion showed improved properties; however, including a higher ratio of zein in the solid dispersion adversely affected the disintegration and release properties of formulations.

Key words: Solid dispersion, Dasatinib, Zein, Bioavailability, Dissolution, Disintegration

INTRODUCTION

An increasing number of oral chemotherapy agents has emerged in the last decade. This treatment approach is appropriate for schedule-dependent agents that may need to be administered daily for months or years, compared to intermittent, short-term conventional antiproliferative or cytotoxic agents that are often administered intravenously [1-3]. Many oral drug candidates have been reported to exhibit low solubility and poor bioavailability after dosing. Approximately 75% of the new drug candidates correspond to classes II and IV in the biopharmaceutical classification system (BCS) [3, 4]. Solubility is an essential factor to achieve the desired drug concentration in the blood for a therapeutic response [3-5]. Orally administered antitumor agents usually exhibit pH-dependent solubility and are often characterized as BCS class II, that is, weak, basic drugs that dissolve in acidic pHs and precipitate in the small intestine [5, 6]. Unfortunately, the bioavailability of these agents is reduced by the co-administration of antacids to alleviate gastroesophageal reflux and gastric inflammation [4-6]. Examples of agents whose exposure is include imatinib, gefitinib, erlotinib, and dasatinib [5-8].

Dasatinib (Figure 1a) is a second-generation tyrosine kinase inhibitor that is administered to patients

with imatinib-resistant chronic myeloid leukemia and is also used for treating other solid tumors [5-9]. Dasatinib exhibits anti-inflammatory properties, including T-lymphocyte inhibition, and can act as a senolytic agent by selectively eliminating senescent cells via the ephrin signaling pathways to delay cellular aging [7-9]. It is available as a commercial oral tablet and, since it is a BCS class II compound, it exhibits pH-dependent aqueous solubility ranging from 18.4 mg/mL to 0.008 mg/mL at pHs 2.6 and 6 [5-9]. This makes the drug susceptible to gastric degradation or emptying before absorption. Drug levels below the minimal effective concentration at the site of action can lead to treatment failure.

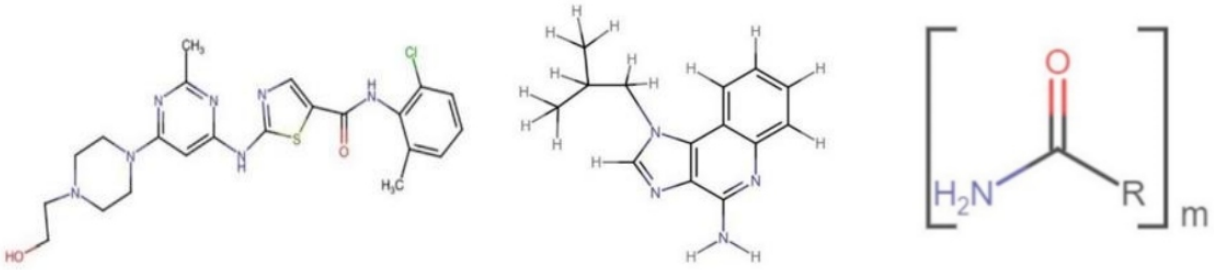

Figure 1. The chemical composition of a) Dasatinib, b) HPMC, and c) Zein.

Improving the solubility of poorly aqueous-soluble drugs is a challenge. To overcome this, the rate of absorption and extent of bioavailability should be improved, which can be achieved by controlling the rate of disintegration and dissolution [3-5]. Techniques such as complexation, micronization, spheronization, salt formation, and solid dispersion (SD) have been used to enhance the solubility of such drugs [1-6]. The latter refers to a group of solid materials that contain one or more active ingredients uniformly dispersed in a solid, inert, water-soluble carrier, or vehicle matrix [4-6, 10-12]. SD has been used for various poorly water-soluble drugs, such as prednisolone [11], nifedipine [12], ketoprofen [13, 14], docetaxel [15], regorafenib [16], and lapatinib [17].

Many materials have been employed as carriers to prepare solid dispersions, such as polymers (β-cyclodextrin, polyethylene glycols, polyvinyl pyrrolidone, hydroxypropyl methylcellulose (HPMC) (Figure 1b) [16-19], surfactants, sugars, and acids [10-19]. Such materials are often employed due to their low toxicity and melting point, fast solidification, and high aqueous solubility. However, water-soluble carriers used in SD usually formed a soft and wet mass that hardly produces tablets [20-22]. These carriers may counter the desired effect by decreasing the dissolution due to the increased viscosity at the boundary layer near the dissolving contact surface [20-22]. This problem can be attenuated by using water-insoluble hydrophilic carriers that deposit the drug on their surfaces. Upon contact with water, the carrier releases the drug immediately. Therefore, the selection of a suitable carrier matrix has a significant effect on the overall dissolution profile of the dispersed drug [20-23].

Protein-based carriers in pharmaceutical formulations provide several advantages such as biodegradability, biocompatibility, and availability of surface area for drug encapsulation [23, 24]. Zein is a natural protein extracted from maize seeds (Figure 1c). The U.S. Food and Drug Administration has classified zein as “generally recognized as safe” because this prolamin protein is composed of 75% lipophilic and 25% hydrophilic amino acid residues [21-23]. This structure may be responsible for its insolubility in water alone; however, it is soluble in binary aqueous solvents that contain fewer aliphatic alcohols, such as ethanol or isopropanol [21-23]. This hydrophobic feature has allowed zein to be successfully employed in tissue engineering scaffolds, targeted and controlled drug delivery systems, and nanocarriers, particularly for poorly water-soluble drugs [20-25]. Various studies recommend using

zein as an alternative tablet excipient to traditional matrix polymers that are produced by chemical modification or synthesis [20-29]. Nguyen et al. [23] studied the inclusion of zein in a solid dispersion system to improve the drug dissolution rate of poorly soluble prednisolone in low-pH media [11]. Another study investigated the role of surfactants in zein–HPMC solid dispersion [26]. The study found that the combination of zein–HPMC solid dispersion with surfactants improved drug dissolution by increasing wettability and crystal changes. However, the comprehensive characterization of zein as an excipient in the aforementioned solid dispersion has not been explored.

In this study, we investigated the potential use of zein in an SD mixture that was directly compressed into tablets with other excipients and dasatinib as a drug model. This system within system (solid dispersion within a tablet) was developed to improve the dissolution of BCS class II oral chemotherapeutic agents.

MATERIALS AND METHODS

Materials

Dasatinib monohydrate was purchased from MedChem Express (Monmouth, NJ, USA); USP-compliant zein from Qingdao Sigma Chemicals Co., Ltd. (Qingdao, China); fasting-and fed-state simulated gastric fluid (FaSSGF and FedSSGF) media from Biorelevant (London, UK); and magnesium stearate, HPMC, ethyl cellulose (EC), and lactose from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals and solvents were obtained from Sigma Aldrich (St. Louis, MO, USA), were of analytical grade, and were used without further purification.

Methods

Preparation of Zein–HPMC Sds

A spray drying-based solvent evaporation method was used to prepare SDs [26]. To evaluate the improvement in the dissolution rate of the SDs, different ratios of each polymer were used (Table 1); this was to investigate the role of the different ratios in achieving a controlled release rate from the tablets. Zein (a hydrophobic polymer) was slowly dissolved in 90% ethanol, under magnetic stirring (LabTech, Seoul, Korea), to obtain a translucent solution. HPMC 4000 (a hydrophilic polymer) was slowly injected into hot water (60 °C) to form a swelling polymeric solution, which was then transferred to cold water (-4 °C) and mixed until a transparent solution was formed. Dasatinib was dispersed into the two solutions under continuous stirring for 30 min. Finally, all the components were placed in a mini spray dryer (Buchi, Flawil, Switzerland) at predetermined settings. The prepared solid mass of SD was stored in a desiccator until further use.

Table 1. Compositions of different powders used in SD preparation.

SD No.	Zein (mg)	HPMC (mg)	Dasatinib (mg)	Total (mg)	Ratio
SD1	30	-	20	50	3:0:2
SD2	-	30	20	50	0:3:2
SD3	15	15	20	50	1.5:1.5:2
SD4	20	10	20	50	2:1:2

Abbreviations: SD, solid dispersion; HPMC, hydroxypropyl methylcellulose; and mg, milligram.

Preparation of drug–excipient powder blends

Excipient powders were sieved using a vibratory sieve shaker (Preiser Scientific, St Albans, WV, USA; sieve No. 40 and 60) to reduce the particle size and eliminate any large, non-uniform particles outside the 150–426 µm threshold. They were then weighed separately on an electronic balance (Mettler Toledo,

Columbus, OH, USA) according to the suitable tableting quantities required. The excipient powders were mixed using an automatic Vblender (ERWEKA GmbH, Langen, Germany) for 10 min and placed in the b290 mini spray dryer at predetermined conditions. Finally, the powder blends of SDs were added to the spray-dried co-excipients for 5 min. The compositions of all the blends are listed in Table 2.

Table 2. Compositions of the prepared dasatinib-zein SD tablets

	Formulations				
Component (mg)	F1	F2	F3	F4	F5
SD1 (zein + dasatinib)	80	-	-	-	-
SD2 (HPMC + dasatinib)	-	80	-	-	-
SD3 (zein + HPMC + dasatinib)	-	-	80	-	-
SD4 (zein + HPMC + dasatinib)	-	-	-	80	-
Ethylcellulose	7	7	7	7	9.5
Lactose	12.5	12.5	12.5	12.5	90
Magnesium stearate	0.5	0.5	0.5	0.5	0.5

Abbreviations: SD, solid dispersion; HPMC, hydroxypropyl methylcellulose

Particle size measurement

The particle size of each SD powder blend was determined using laser diffraction (Zetasizer Nano, Malvern, UK). Each spray-dried powder blend was added to a cuvette that was filled and mixed with phosphate-buffered saline. All measurements were performed in triplicate.

Tablet preparation

Tablets were directly compressed [20]. Briefly, the quantities of each component (Table 2) were obtained from the automatic V-blender, and the tablets were accurately weighed using the electronic balance (Mettler Toledo). The powders were compressed using an ERWEKA GmbH instrument (Germany) with a force of 60–80N and round punches. The lubricant magnesium stearate was added to the mixture in the final step.

Tablet hardness, thickness, and tensile strength

The dimensions of individual tablets were measured using a Vernier caliper (Swastik Scientific, Mumbai, India); the hardness of individual tablets (from the different formulations) (Table 2) was determined 24 h after compression (allowing for stress relaxation) using a tablet hardness tester (Horsham, Mecmesin, UK), which applies force from two oppositely situated metal anvils. The digital screen displayed the hardness required to break the tablets in kg/cm2. The tensile strength (T) of each tablet was calculated using the formula:

$$T = \frac{0.0624\ X\ Hardness\ (P)}{Diameter(\mathrm{D}) X\ Thickess\ (L)} \quad (1)$$

Tablet friability

This test measured the friability of the tablets by determining the percentage weight loss during the rotations inside a Roche friabilator (Copley, Nottingham, UK) [30-33]. Twenty pre-weighed tablets were initially placed in the friabilator. The friabilator was then rotated 100 times over 4 min. Once finished, the tablets were gathered, dusted, and reweighed, and this value was considered the final weight. Percentage weight loss was calculated using the formula:

$$\text{Percentage of weight loss} = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100 \quad (2)$$

Tablet weight variation

For each formulation type (Table 2), 20 tablets were randomly selected and weighed individually using the electronic balance (Mettler Toledo), from which the average weight was determined. The average weight was calculated, and the weight of the individual tablet was compared to the average weight. The upper and lower limits at % and double % differences were calculated and compared to the individual weights of the tablets.

Drug content analysis

A validated UV spectrophotometer was used to analyze the dasatinib content in the tablets [27]. First, a calibrated standard curve for dasatinib was used as the reference. A stock standard solution containing dasatinib was prepared by dissolving 100 mg of the pure drug in 250 mL acetic acid in a calibrated flask. The working solution (0.04% w/v) was used for spectrophotometric analysis (S-2150UV spectrophotometer, Dayton, NJ, USA). Briefly, different aliquots of the standard drug solution were transferred into calibrated flasks that contained 3 mL of acetate buffer (pH 4) and 1% Triton X-100 and mixed well. Absorbance was measured at 323 nm against a blank. The absorbance values were plotted against the drug concentrations to obtain a calibration curve. The tablets were then crushed and mixed thoroughly in 70 mL of acetate buffer (pH 4) and 1% Triton X-100 (Sigma-Aldrich). The resultant solution was filtered using filter paper (Hawach Scientific, Xi'an City, China), and 1 mL of the filtrate was collected and diluted to obtain the desired concentration of 10 µg/mL.

Tablet disintegration

Six tablets of each formulation (Table 2) were placed inside different tubes of a basket disintegration test apparatus (Caleva, Struminster, UK). The baskets were then placed inside beakers containing a suitable volume of distilled water and FaSSGF and FedSSGF media at 37 ± 0.5 °C. The time required for full tablet disintegration was recorded.

In vitro dissolution studies

This experiment was performed using a USP dissolution tester apparatus II (PTWS 820-MA; Hainberg, Germany). The paddle was rotated at 60 rpm at 37 ± 0.5 °C. Each type of tablet presented in Table 2 was exposed separately to 900 mL of FaSSGF and FedSSGF media, and distilled water was used as the control. Samples of 5 mL for each tablet type were withdrawn at predetermined intervals (starting from 0 min until 60 min) and replaced with fresh medium to maintain a constant dissolution volume. To filter the withdrawn samples, a Whatman filter paper grade 1 was used. The concentration of dasatinib was analyzed using spectrophotometry model S-2150UV (Dayton, NJ, USA), and expressed as a percentage of the drug dissolved.

Statistical analysis

The results were acquired in triplicate and analyzed using the student's t-test or one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison procedure, using Prism GraphPad version 7.3.1 for Windows (GraphPad Software, San Diego, CA, USA). The results are presented as the mean ± standard deviation (n = 6). Statistical significance was set at $P < 0.05$.

RESULTS AND DISCUSSION

Preparation of Zein–HPMC SDs and excipients

Zein and HPMC were added to achieve a high degree of dasatinib dissolution in the gastric environment. HPMC also acts as a super disintegrant [17-19]. Spray drying has been used successfully to produce excipients with superior properties compared to physical mixtures. In this study, the excipients used were well-known components of most co-processed excipients; they are considered excellent and directly compressible excipients [20, 21]. Zein was used as the hydrophobic portion of SD, while HPMC was the hydrophilic portion and disintegrant. EC, lactose, and magnesium stearate were used as the binder, filler, and lubricant, respectively.

Particle size analysis

Drug particle size is known to notably affect drug dissolution rate, thus size reduction is important. Table 3 shows the particle size distributions of the various preparations composed of zein SDs and zein SDs/excipients. The particle size distributions of the spray-dried powder blends were significantly smaller than those of the physical mixture. It was observed that the range of the physical mixtures of all the formulations was 262.4 ± 3.5 and 539.2 ± 0.5 µm, which was further reduced to 107.3 ± 3.1 and 190.5 ± 0.5 µm when the physical mixtures were spray dried. There was a significant difference (P=0.002) in favor of all the spray-dried preparations, regardless of the compositions.

Table 3. Particle size distribution of the zein SDs and zein SDs/excipients (mean± SD, N = 3)

Preparations	Particle Size (µm) Physical Mixture of Powder	Particle Size (µm) Spray-Dried Powder
F1	310.5 ± 1.4	190.5 ± 0.5*
F2	420.3 ± 1.2	107.3 ± 3.1*
F3	343.6 ± 3.4	129.3 ± 3.4*
F4	539.2 ± 0.5	152.9 ± 2.7*
F5	262.4 ± 3.5	160.2 ± 1.5*

*Mean P-value was found to be equal to 0.002 or less

Abbreviation: SD, solid dispersion

Tablet hardness, thickness, and tensile strength

The average hardness of the zein tablets was similar to the official range of hardness stated in the USP guidance, which is not less than 4 kg of pressure required to break a tablet [27, 28, 30, 34]. The average thickness of the dasatinib tablets was also following the USP guidelines. The tensile strength of the formulations showed an average of 1.02 ± 2.1 to 2.13 ± 3.1 MPa, as shown in Table 4.

Table 4. Zein SD tablets' hardness, thickness, tensile strength, and friability (mean ± SD, N =3)

Tablet	Hardness (kg)	Thickness (mm)	Tensile Strength (MPa)	% Friability
F1	2.9 ± 1.5	5.2 ± 0.3	1.02 ± 2.1	3.80 ± 1.55
F2	4.1 ± 0.5	5.2 ± 0.3	2.13 ± 3.1	1.20 ± 0.75
F3	3.4 ± 0.4	5.2 ± 0.3	1.83 ± 1.2	0.71 ± 0.15
F4	3.5 ± 0.2	5.2 ± 0.3	1.89 ± 2.1	0.82 ± 0.42
F5	3.7 ± 0.2	5.2 ± 0.3	1.42 ± 1.2	1.32 ± 0.45

Abbreviation: SD, solid dispersion

Tablet friability

Table 4 shows the average percentage of weight loss for each tablet type. Only the tablets containing HPMC alone or excipients were found not to be compliant with the permissible USP guidelines (less than 1%). In contrast, the F3 and F4 tablets were within the permitted USP range of friability, as reported previously [31-33].

Tablet weight variations and drug content assay

A weight variation test was performed to ensure tablet uniformity [31]. The weight variation test indicated that the average weight of the tablets was in accordance with the USP requirement that no more than two tablets out of 20 tablets should cross a ±10% deviation (Table 5). Similarly, the zein SD tablets were within the range of the upper and lower limits, where the average weights of 20 tablets of F3 and F4 (containing dasatinib with different ratios of zein and HPMC) were 106.5 ± 0.41 and 103.7 ± 0.24 mg, respectively. This indicated a statistically significant difference between the two formulations in favor of F4 ($P < 0.02$). However, both formulations were within the allowable limits for tablet weight in accordance with the UPS recommendations.

Table 5. Zein SD tablets' weight variations and drug content (mean ± SD, N = 3)

Tablet	Weight (mg)	% Drug Content	Disinteg. Time (min) D.W.	Disinteg. Time (min) FaSSGF	Disinteg. Time (min) FedSSGF
F1	112.9 ± 0.32	90.16 ± 1.45	98.1 ± 2.95	60.2 ± 5.7	50.9 ± 3.1
F2	134.1 ± 0.11	92.14 ± 1.56	25.2 ± 5.67	41.6 ± 4.3	30.5 ± 2.2
F3	103.7 ± 0.24	94.11 ± 3.45	75.5 ± 3.30	40.3 ± 4.2	35.5 ± 3.6
F4	106.5 ± 0.41	93.21 ± 1.25	71.7 ± 5.70	50.5 ± 2.7	39.1 ± 2.9
F5	109.3 ± 0.51	4.20 ± 1.20	15.8 ± 2.30	10.5 ± 3.7	13.5 ± 3.3

[1] Abbreviations used in Table 5: Disinteg. Time, disintegration time; D.W., distilled water; FaSSGF, fasted-state simulated gastric fluid; FedSSGF, fed-state simulated gastric fluid.

Dasatinib content was measured using a validated UV spectrophotometer. The percentage drug contents of all the tablets (except F5, which contained no drug at all) were found to be in the range of 90.16 ± 0.45 to 94.11% of the expected drug content, which was within the acceptable USP limit [31, 32], as shown in Table 5.

Tablet disintegration assay

The disintegration behaviors of the produced tablets in the fasted and fed-state gastric media are shown in Table 5. Gastric media in both states (fasted and fed) were used because dasatinib is a weak base that dissolves well in acidic pHs and precipitates in the small intestine [5-9, 32, 33, 35]. All the tablets that contained zein required a longer time to disintegrate in distilled water compared to those that contained HPMC only (F2) or excipients only (F5). In contrast, the disintegration time was significantly reduced in the tablets containing zein and HPMC SDs, in both states of the simulated gastric media (Table 5).

In vitro dissolution studies

In vitro drug dissolution studies were used to simulate the in vivo behavior of the tablets to predict the in vivo performance if the conditions of the studies are feasible [30, 33, 35]. The dissolution profiles of pure dasatinib and zein-HPMC-based SDs in different media are shown in Figure 2. In distilled water, the F1 tablets, which contained zein SDs (without HPMC), showed the lowest percentage release rate (approximately 15.2% ± 2.5). The same formulation showed a release rate that more than doubled over

time (43.7% ± 8.3 and 47.7% ± 8.3, respectively) when placed in both gastric simulated media (Figure 2a). In contrast, the F2 tablets containing HPMC SDs alone showed increasingly higher percentages of release over time in all the media and reached an average of more than 90% by the end point of the experiment, as shown in Figure 2b. Meanwhile, the F3 tablets, which were composed of SD3 (zein and HPMC SDs in the ratio of 1.5:1.5:2) and dasatinib, demonstrated significantly improved release characteristics over time in both states of the gastric medium. The percentage of dasatinib release reached 76.70% ± 2.60, 76.70% ± 13.6, and 79.70% ± 10.45 in DW, FaSSGF, and FedSSGF, respectively, by the end of 60 min. Similar results were observed with the F4 tablets, which contained zein and HPMC SDs in the ratio of 2:1:2, and dasatinib, which achieved more than 80% drug release in both states of the gastric medium. Although the dissolution rate improved in the DW medium for all the formulations, a better dissolution rate was still observed in both states of the gastric medium.

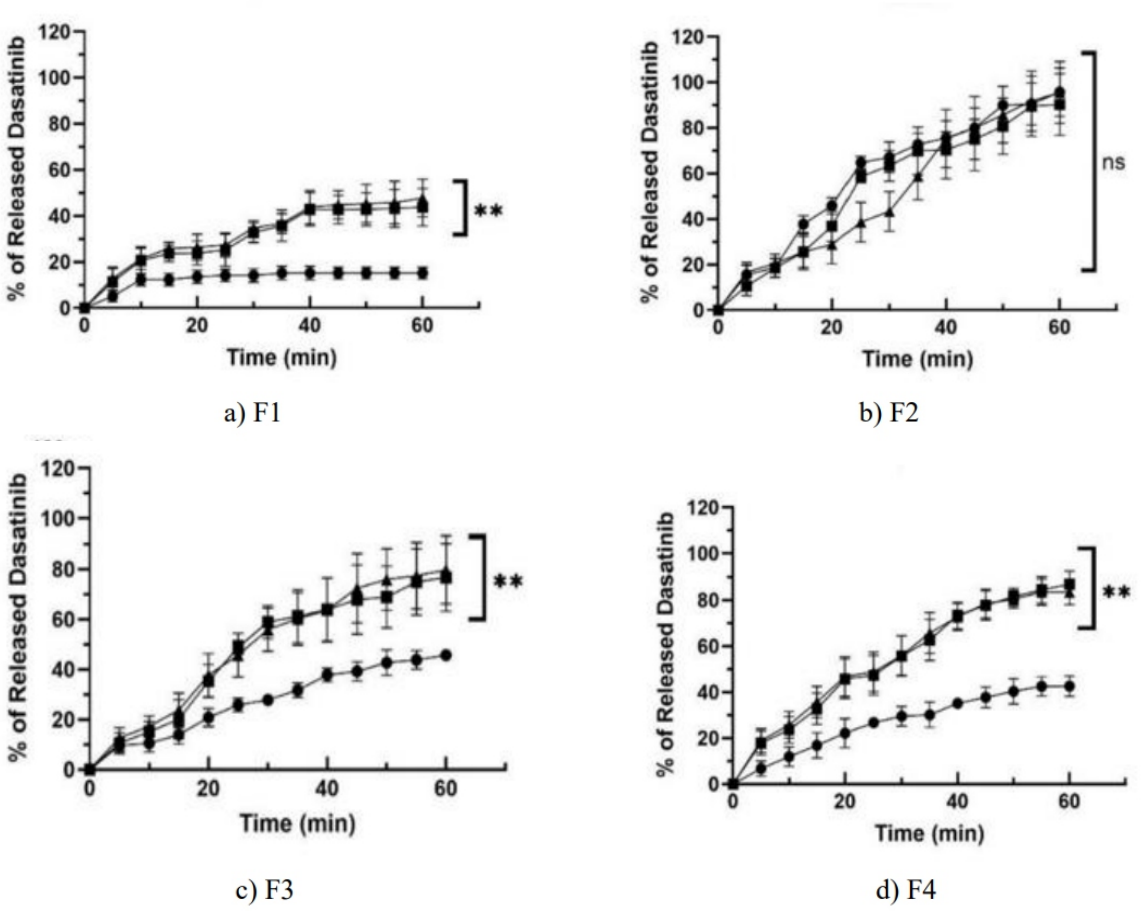

Figure 2. Dissolution profile of zein–HPMC SD tablets containing dasatinib. ns= no significant difference between the formulations. ** mean P-value < 0.05.

Solid dispersion is a well-known technique used to improve poor drug dissolution and bioavailability, particularly in drugs used for cancer treatment [10-16]. However, SD components play a major role in the treatment effect. Herein, natural hydrophobic prolamin zein, accompanied by hydrophilic HPMC, was utilized to prepare spray dried SD powders. Different ratios of both components were used to determine the optimal ratio that would yield the most desirable characteristics. Zein is a promising natural pharmaceutical excipient because of its unique alcohol solubility and poor aqueous solubility, which consequently provides flexible deformation in polar solvents [28]. Furthermore, zein can reduce the photolytic degradation of the drug and lessen the harsh gastric pH [27, 28]. Conversely, HPMC is a

well-known biodegradable hydrophilic polymer used to enhance the solubility of active pharmaceutical ingredients (APIs). Herein, it also contributed to further enhancing the compatibility of the coprocessed excipients. Both zein and HPMC were added to achieve a high degree of controlled dasatinib release in the intestinal environment. Moreover, an excipient combination was added to the SD mixtures during the spray drying process to produce more stable co-processed excipients with enhanced properties compared to the physical mixture. The excipients used herein were excellent directly compressible excipients [20, 22]. The excipients included a binder, filler, and lubricant, which facilitated the compaction process and enhanced the physical stability of the tablets.

The spray-drying technique is commonly used to produce typically small particles (10–100 μm), which allows them to rapidly disperse in a proper medium [10-16]. In all the preparations, the average sizes of the different zein SDs prepared by spray-drying were less than half of those of the physical mixture, indicating a significant size reduction, compared to the physical mixture, of the SD blends. The smaller particle size of the spray-dried zein–HPMC SD powders compared to the physical mixtures agrees with the literature, which notes that the spray drying technique reduces agglomerated particle size [11, 12]. Consequently, this increases the surface area of the SDs to be occupied by the co-processed excipients. Therefore, the small particle sizes of the various zein–HPMC SDs successfully facilitated the disintegration and dissolution of dasatinib.

The blends of zein–HPMC SDs and other excipients were evaluated for hardness, thickness, tensile strength, and friability. The various types of tablets were mostly within acceptable USP limits as reported in several studies [27, 28, 30, 34]. This indicated that the zein–HPMC SD tablets were mechanically stable (Table 5). However, the tablets containing HPMC alone or excipients were not compliant with the permissible USP guidelines for tablet friability (less than 1%) [28, 30-32, 34]. Conversely, the F3 and F4 (containing different ratios of zein and HPMC) tablets were able to withstand the mechanical stress produced during the friability test. Collectively, the current data support the feasibility of zein as a suitable matrix for tablets [27, 28, 30, 34]. However, zein cannot be used as an excipient on its own and requires other functional excipients to improve tablet integrity. Therefore, other components or excipients must be included in zein formulations.

The results of all the developed formulations were within the acceptable ranges reported in the official compendia (Tables 4 and 5). This indicated the consistency of tablet compression between the tablets, which may be due to the stability of the spray-dried SD powder blends used herein. Generally, the tablet weight had a direct influence on the drug content within the tablets, which was reflected in the similarly high content of dasatinib in all the formulations (except F5) (Table 5). This result also indicated that the SD powder blend, dasatinib, and excipient distributions were homogenous [10, 11]. The disintegration times obtained for all the formulations were significantly different, depending on the medium used for the disintegration test. The disintegration time was shortest in the following order: FedSSGF medium > FaSSGF > DW. This order is compatible with the fact that zein is poorly soluble in water, but it seems that the zein–HPMC SDs and other excipient blends enhanced the disintegration of all the formulations. Contrastingly, the disintegration of all the formulations was significantlyreduced in both states of the gastric simulated media (fasted and fed), but the formulations favored the fed state, where disintegration occurred in <40 min. This substantially shorter disintegration time of the tablets prepared using the zein and HPMC complex implied that the formation of a solid dispersion of zein and HPMC facilitated de-agglomeration and did not prevent acidic media ingress. It appears that this composition of tablets favors fasted-state disintegration more than fed-state disintegration.

The dissolution profiles of all the tablets were analyzed (Figure 2). Owing to the low solubility of zein and dasatinib in aqueous media, it was expected that a low percentage of release would be achieved in the DW medium compared to that in the other gastric media. However, the combination of the zein–HPMC

SD with suitable excipients significantly improved release across all the aqueous and gastric media used herein. A comparison of the F1 and F2 formulations indicated that the inclusion of water-soluble HPMC in the zein SD (F2) successfully enhanced the dissolution rate of dasatinib. This is because of the higher solubility of HPMC in water, along with some of the other excipients used herein. The presence of zein–HPMC SDs in the F3 and F4 formulations improved their dissolution profiles, which demonstrated a gradual increase within the first 45 min, regardless of the zein amount used. Generally, the trend for the dissolution rate was similar to that of disintegration in terms of favoring the fed-state gastric medium. However, increasing the amount of zein can adversely prolong the dissolution, which in turn limits the extensive use of zein as an excipient.

CONCLUSION

From the present study, it can be concluded that the solubility of the oral chemotherapeutic dasatinib can be successfully improved by formulating the drug into a solid dispersion that includes zein, HPMC, and other excipients. Hence, zein–HPMC SD may be considered a suitable alternative for formulating poorly soluble therapeutic agents into tablets that have improved gastric absorption, which is a requirement for enhanced bioavailability.

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Healthy Schools Framework in Saudi Arabia: A Narrative Review

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ABSTRACT

The Healthy School (or Health-Promoting School as a term used by WHO and other countries) is a whole-school approach to promoting health in a school setting. Healthy Schools and Health-Promoting Schools frameworks extend around the globe are important strategies that provide opportunities to improve the health of children and adolescents and to tackle health inequalities in the population. Two decades since the Healthy Schools framework was advocated in Saudi Arabia. This paper sets out to review relevant literature and reports related to Healthy Schools in Saudi Arabia. Very few studies have been conducted to assess the Health Schools framework. The findings showed that there is a gap between the ideal concepts of the Healthy Schools framework and current implementation. Promoting healthy diet and physical activity as a starting point for wider implementation. Providing financial resources and ongoing capacity-building opportunities for the teachers and associated school staff. Collaboration between the health and education sectors is required to provide a prolonged framework for monitoring and evaluating the healthy schools outcomes.

Key words: Healthy school, Health-promoting school, School health promotion, School health

INTRODUCTION

Children and adolescents need to have opportunities to maintain their health to learn in safe and healthy environments. Healthy children gain better academic achievements which, are associated with improved health in adulthood [1]. Experiences during the early years including access to education and health are considered crucial for a person's later development [2]. In addition, most premature deaths and disabilities are related to preventable health behaviors that are often adopted at an early age and extend into adulthood [3].

Schools provide a way of reaching many children and adolescents, and they are encouraging settings for promoting health [4]. Many health promotion initiatives have been developed to equip schools to promote the health of their students, teachers, and local communities. Health promotion in schools provides opportunities to improve the health of children and adolescents and to tackle health inequalities in the population. Healthy Schools and Health-Promoting School frameworks spread around the globe as important approaches for promoting health in schools. In Saudi Arabia, it has been two decades since the Healthy School framework was advocated. Therefore, this paper sets out to review relevant literature and reports related to Healthy Schools in Saudi Arabia.

Health-promoting school initiative

The health-Promoting School initiative was first recognized at a World Health Organization (WHO) European Conference in Scotland in the early eighties. It has since been advocated as an effective framework for health promotion in the school setting [5]. In 1986, the Ottawa Charter for Health Promotion provided a ground for schools to be considered as settings for enabling children and adolescents to be healthy and empowered, and linked to families and communities. In consistency with this direction, in 1995 WHO launched the Global School Health initiative to involve more schools that can be described as "Health-Promoting Schools". WHO defined a Health-Promoting School as "a school that is constantly strengthening its capacity as a healthy setting for living, learning and working"

[6]. Other terminologies, such as Healthy School and Comprehensive School Health, share the essential elements of Health-Promoting Schools. These elements include healthy school policies, health education, school physical environment, school medical care services, the social environment of the school, and partnerships with family and community [7, 8] (Table 1). Therefore, Health-Promoting School has been described as a whole-school approach to promoting health that recognizes the holistic view of the interrelationship between health and education [9].

Table 1. Key elements for Health-Promoting School framework [8]

Element	Indicators
Healthy Policies	Healthy food & healthy canteen Physical activity Save & Secure setting environment
Healthy Physical Environment	Students' safety Fire safety & Control emergencies Healthy setting for students & staff
Healthy Social Environment	Supportive care and trust environment Encouraging positive attitude & behavior Prevent & control unacceptable behavior
Health Education Skills	Ensuring opportunities for all students to actively engage in the health topic Providing training for teachers in health promotion & developing healthy school Providing health education resources for students& teachers
Links with Community	Involving families & local community people in school activities Consults surrounding community people for advice on Healthy School development
Health Care Service	Providing emergency & primary medical care services Early medical screening

The WHO Health-Promoting Schools initiative offers a mechanism for the integration of different elements that combined education and health [10]. The initiative undertakes four ways in creating Healthy Schools: building the capacity to advocate for enhanced school health activities; building networks and alliances for the development of Health-Promoting Schools; supporting national capacities; and encouraging research to improve school health outcomes [6].

Research shows that learning and health are interconnected; healthy children are likely to gain better learning outcomes [7]. The health-Promoting School framework has been shown to have clear benefits for health and education [11]. Moreover, there are overwhelming pieces of evidence to demonstrate that the Health-Promoting School framework is effective in improving the school's hygienic environment, physical activities, healthy eating, mental health, and health policies [9]. Cochrane analysis of the Health-Promoting School framework showed benefits in some aspects like reduction in students' Body Mass Index, improvement in physical activity, increase in the consumption of fruits and vegetables, decrease in cigarette smoking, and decrease in incidents of bullying [12]. In addition, Lee et al. [11] identified key indicators with high significant impact on a wide range of health aspects among students. Those key indicators can be considered as another key education objective. In a systematic review conducted by Stewart-Brown [13] to assess the effectiveness of the Health-Promoting School framework in improving the well-being and health of children and adolescents; he argued that there is evidence to support the effectiveness of some aspects of Health-Promoting School. Moreover, Leger et al. [14] showed in their review the effectiveness of health promotion interventions in improving students

health behaviors and wellbeing.

The Health-Promoting School framework has been implemented in many countries. In Europe, The European Regional Office of the WHO, the Council of Europe, and the Commission of the European Communities jointly established the European Network for Health Promotion Schools [5]. In North America, the Comprehensive School Health Program principle is more common than the Health-Promoting Schools [15]. Also, other networks were launched such as; the Australian Health Promoting Schools Association [16], the Western Pacific Region of the WHO [8], Asia, The Middle East, Africa, and Latin America [17]. Although the literature shows that implementation of the Healthy Schools or Health-Promoting Schools framework varies between countries, three key domains were commonly adopted: health education curriculum; healthy physical and social environments of the school; and interaction between the school and the local community.

Health-related status in Saudi Arabia

The population in Saudi Arabia exceeds 34 million and is at an early stage of transition into aging [18]. The report of the 2019 World Health Survey in Saudi Arabia showed that 93 % of respondents have insufficient intake of fruits and vegetables, 80% have insufficient physical activity, and 12% were current tobacco smokers (20% in males and 2% in females). The prevalence of overweight and obesity were 38% and 20%, respectively. The percentage of respondents with raised serum cholesterol was 43% of respondents. Overall, the percentage of respondents with low hemoglobin was 50%, and approximately 14% of respondents have raised blood pressure [19].

On the other hand, more than one-third (32%) of the population in Saudi Arabia is in the 0-19 dependency age group [18]. Research shows that children and adolescents have a considerable prevalence of unhealthy behaviors. In a large national survey among school students, across all the Saudi Arabia regions, 12,575 adolescents participated [20]. The results of the survey showed that 28 % of adolescents have a chronic health problem, 14% have symptoms of depression, thirty percent are overweight or obese, more than ninety-five percent have vitamin D deficiency, 15 % were underweight, and ten percent were anemic [21]. In addition, various unhealthy behaviors such as; tobacco use, unhealthy diet, physical inactivity, violence, insufficient safety precautions, and bullying, were extremely prevalent [20]. Regarding dietary behaviors, only 55% were found to consume breakfast daily, 54% had at least one serving of fruit/vegetable intake per day, 38% reported drinking at least two sugary drinks, and 22% drank one energy beverage daily. Regarding physical activity, almost 50% of boys were physically inactive, the higher absence of physical activity was among girls, and 40% of adolescents spent 2 hours per day watching television [22]. Regarding behaviors related to traffic safety, only 14% reported seat belt use sometimes or always, and 35% had ever been in a road accident. Regarding bullying and violent behaviors, 25% reported exposure to bullying at school during the 30 days preceding the study, and 20% were involved in physical violence at school or community during the preceding year. Concerning tobacco and substance use, 16% had ever smoked cigarettes, and Sixteen percent reported solvent sniffing in the preceding month. Lastly, bronchial asthma was the most prevalent with 29%, and 24% of adolescents reporting difficulty in access to health care services [20].

Healthy schools in Saudi Arabia

Almost twenty years since the Health-Promoting Schools initiative was advocated in Saudi Arabia. In 2002, the Health-Promoting Schools framework was adopted, and during that time, two phases were completed. In phase one, the Health-Promoting School framework was introduced to School Health Departments in the regions through several meetings and workshops [23]. In 2003, School Health Departments in the regions started the pilot phase by implementing a Health-Promoting School

framework in one of their schools. The pilot phase recruited nearly 72 schools. The Health-Promoting Award Scheme was set to guide and improve the implementation of the framework. It covered eight elements: school health services; health education for students; school environment (physical and social); health education for school staff; relations with the surrounding community; food safety; physical activity; mental health; and counseling services [24].

Very few studies have been conducted to assess the Health-Promoting School framework in Saudi Arabia. A survey by Alzahrani [25] looked into the progress and experiences in implementing Health-Promoting Schools across Saudi Arabian regions. The key findings of the survey emphasized the significant increase in the number of schools that implemented the Health-Promoting School framework. The percentages of schools that implemented the Health-Promoting School framework were 65% of primary schools, 21% of intermediate schools, and 14% of secondary schools. The core perceived strengths of the Health-Promoting School framework were increasing the health awareness of students and improving the schools' physical environment. The most common activity addressed was traditional health education. Schools' social environment and health policy were not among the key elements of the Health-Promoting School Award Scheme. The main weaknesses were a lack of financial resources and professional training. Lastly, there was a limitation in the evaluation of HealthPromoting School elements.

In Makkah city, Elamin et al. [26] conducted a study to assess the implementation of seven components of the Health-Promoting School framework. They found that eighty percent of the targeted activities in Health promoting Schools were health education activities. In addition, 85 % of healthy school environment requirements were achieved. Large improvements in students' behaviors were considered great achievements. The main weaknesses were limitations in canteens' food services, lack of medical care services in schools, and the absence of school links with local communities.

Another survey was conducted in the Qassim region to evaluate the implementation of the Health-Promoting Schools framework from the perspective of teachers who supervised the program in the schools. The respondents reported the need for expanding the program's implementation, more training for teachers, increasing incentives, and financial support [27].

Similarly, another study was conducted in the Aseer region to assess the Health-Promoting Schools framework from the perspectives of program supervisors in the schools. The supervisors reported there was a need for expanding the program's implementation and increasing the financial resources [28].

RESULTS AND DISCUSSION

The World Bank report for Saudi Arabia indicates that economic and nutrition transitions in Saudi Arabia have increased the incidence of diabetes by 94 %, heart diseases by 54 %, cancers by 50 %, and chronic respiratory diseases by 48 % among the working-age population [29]. The major risky behaviors (smoking, unhealthy diet, and physical inactivity) contribute to the occurrence of the four major non-communicable diseases in Saudi Arabia [29]. Research shows that most behavioral risk factors adopted in adulthood are almost initiated in early life [3]. In addition, healthy behaviors can be established in children and adolescents, and these behaviors tend to become a healthy lifestyle in later life. There is real concern about the escalating trend of unhealthy behaviors among children and adolescents in Saudi Arabia such as smoking tobacco, physical inactivity, sedentary habits, and unhealthy diet (less consumption of vegetables and fruits, and high consumption of sugars). And most of these behaviors play a key role in the pathogenesis of obesity in children and adolescents [30-32]. The Health-Promoting School has been identified as the most effective approach to promoting healthy behaviors in children and adolescents which, in turn, improves development and health in later life [7]. Although the Healthy School framework in Saudi Arabia has been adopted for promoting health among children and

adolescents, studies showed that there is a gap between the ideal concepts of Healthy Schools and current implementation. Moreover, the sustainability of a Healthy Schools framework has not yet been achieved. Therefore, there is an urgent need to reinforce this approach at a high level in both the health and educational sectors. The health and education authorities need to collaborate effectively to implement a Healthy Schools framework.

CONCLUSION

As a starting point, every school in Saudi Arabia should have a supportive and attractive infrastructure for the learning and health of students. In addition, the key elements of a Healthy School framework are needed as a starting area for wider implementation. More specifically, the health promotion interventions for a healthy diet and physical activity. Promoting a healthy diet includes healthy food and drink policy, and a healthy school canteen (a canteen that provides healthy food choices). Promoting physical activity includes organized and non organized physical activities, providing a playground and time for playing cooperative sports games. Moreover, developing a national Healthy School framework scheme and comprehensive monitoring and evaluation tool for the Healthy School's framework is essential and needs collaboration between both the education and health sectors. Lastly, providing financial resources and ongoing capacity-building opportunities that complement the fundamental role of the teacher and associated school staff.

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A Review of the Protective Effects of Nanoparticles in the Treatment of Nervous System Injuries

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ABSTRACT

One of the most vital organs in the body is the nervous system. Damage to the nervous system may lead to a variety of issues and illnesses in people, and each year, both the affected person and society incur significant financial, human-life, and spiritual expenses as a result. Although the activity in the field of nerve repair and regeneration is growing rapidly, until now, nerve repair is not done completely. A chain of events, including inflammation, elevated oxidative stress, and the progression of damage, occur after the initial insult to the nervous system. Damage to mitochondria, proteins, and cell membrane structures, damage to adipose tissue, and eventually illnesses of the nervous system can all be a result of oxidative stress, which is brought on by an imbalance between the creation of free radicals and metabolic responses. As a result of inadequate antioxidant levels or excessive formation of free radicals, damage to nerve cells might worsen. Nerve cells require a lot of oxygen and antioxidants. To stop oxidative stress and its harmful consequences, antioxidants—either synthetic or natural—must be used. In this context, the treatment of illnesses of the neurological system may hold promise for nanoparticles with a long half-life. As a result, the biological use of nanoparticles has been stressed as a novel therapeutic strategy for the treatment of neurological disorders and lesions, which is still in its early phases. Therefore, the purpose of this review is to ascertain how protective nanoparticles are in the therapy of nervous system damage.

Key words: Nanoparticles, Nervous system injuries, Protective effects, Treatment

INTRODUCTION

Peripheral nerves are usually subject to physical damage. Usually, construction and transportation accidents, natural disasters, injuries caused by war, and other traumas such as diseases and complications caused by surgery cause peripheral nerve damage [1, 2]. Following peripheral damage, a series of pathophysiological events occur, which leads to valerian disintegration in the distal part and the loss of a small part of the proximal part of the axon. Together, macrophages, monocytes, and Schwann cells remove the myelin sheath and axon debris. Schwann cells multiply and form a bridge called the band of Bungner [3, 4]. These cells produce extracellular matrix molecules and neurotrophic factors to stimulate axon regeneration [5]. Axon sprouts are formed by the nodes of Rannoia and the new myelin sheath is formed by Schwann cells. Axon sprouts grow until the axon can perform its functions again. Spontaneous repair of the peripheral nerve is almost always incomplete and the function of the nerve does not completely return to its original state [6, 7]. Strokes, head trauma, spinal cord injuries, and retinal degeneration are some examples of central nervous system injuries. These lesions in children are often traumatic or congenital defects, while in adults they are traumatic or degenerative. Following

damage to the central nervous system, events such as the death of nerve cells, destruction of nerve fibers and glycolysis, and an excessive increase in the number of glial cells (such as astrocytes, oligodendrocytes, and microglia) occur. Neurons cannot divide, so if a neuron is destroyed, a new neuron will not replace it, as a result, the central nervous system, unlike the peripheral nervous system, does not have the inherent ability to repair itself [8-10].Regenerative medicine is a branch of modern medical science whose goal is to restore and restore damaged or lost tissue or organs, which, according to the type of treatment approach and method, includes cell therapy, treatment using the patient's cells, treatment using non-autologous donor cells, treatment with growth factors, use of recombinant proteins, use of small molecules, tissue engineering, and gene therapy [11-13].

One of the more recent and useful fields that has caught the interest of academics and offered several chances for advancement in the medical sciences is nanotechnology. This technology is employed in the medical field as well as in the military, agriculture, diagnostic procedures, magnetic imaging, sensors, and fast material detection. These days, scientists employ this technology to identify and treat a wide range of illnesses, including cancer. Thus, by concentrating on molecular techniques, this discipline has gained recognition as a significant branch that has made remarkable developments in recent years [14]. Materials that are utilized in surgery, dentistry, all types of experimental science studies, biomechanical biosystems, the battle against germs, etc. may be created using nanotechnology, which is based on the utilization of atoms and molecules. Scientists currently have little control over the scope of nanoparticle impacts, despite the fact that there have been several studies on the subject [15-17].

Less intrusive techniques are more appropriate for the discussion of imaging methods, making nanoparticles the best possible candidates for the creation of such techniques. In nanotechnology, they utilize specially designed materials that can interact with biological systems at the molecular level and stimulate the nervous system while causing the fewest possible adverse effects. Contrary to conventional systems like pills and liquids, nanoparticles intelligently regulate and sustain the distribution of medications in various organs, resulting in more and better effects [18, 19]. Nanoparticles are used for imaging in neuroscience and also to investigate the fate of adult stem cells in nervous systems and in the treatment of many nervous system disorders [20, 21].

Today, much research is conducted on smart materials that can help in the regeneration and treatment of nerves through various methods such as antioxidant effects, stimulating the proliferation of nerve cells, modulating inflammatory factors, etc. Therefore, due to their chemical and morphological characteristics, some nanoparticles are promising therapeutic methods that can have neuroprotective and antioxidant properties depending on the dose and size [22]. So, the purpose of this study is to look at how nanoparticles might help guard against nervous system damage.

Nanoparticles as new drug delivery systems in the nervous system

Protective barriers make it difficult for biologists to deliver drugs to the central nervous system. Drugs must be able to penetrate the blood-brain barrier and enter therapeutic concentrations in the brain after administration for them to be effective in the central nervous system [23]; otherwise, they won't be able to do their jobs [23]. As a result, ineffectiveness in the treatment of illnesses of the central nervous system is frequently not a result of a medicine's insufficient potency but rather of an issue with the way the drug is delivered. Recently, interesting results have been observed in the field of nanotechnology, particularly when nanoparticles are used to transport drugs [24]. Typically, for a pharmacological therapy to be successful, it has to have a long shelf life in the blood.It is now possible to functionalize the surface of nanoparticles with positively charged biomolecules to create an electrostatic interaction, which facilitates the passage of nanoparticles through the blood-brain barrier because endothelial cells have negative charges on their surface. Transferrin and lipoprotein receptors in the cell allow nanoparticles to

absorb and cross the blood-brain barrier [25]. Additionally, the prolonged circulation of modified nanoparticles in the blood makes it simpler for them to interact with and enter endothelial cells, which opens up the prospect of greater control over the actions of the cells. The use of nanoparticles in medicine is still plagued by issues including unknown tissue interactions and unpredictable outcomes, despite the current advancements in the field of nanoscience. In this context, high-penetrating-power cerium oxide nanoparticles can inhibit the development of scar tissue that hinders healing in spinal cord lesions [26]. As opposed to anionic nanoparticles, cationic nanoparticles are more permeable to the central nervous system and can remain in circulation for extended periods of time without having hazardous consequences. For instance, cationic gold nanoparticles may enter cells without using energy and by avoiding processes like endocytosis, which might have an impact on cell function [27].

Enzyme carriers for antioxidants can be made from nanomaterials. Antioxidant enzymes can lower reactive oxygen species (ROS), but because of their transient presence in the blood and subsequent decomposition, they have a hard time crossing the blood-brain barrier [28]. Polymer nanoparticles are the most common type of medication delivery technology because they can cross cells' tight connections. Additionally, they have a high drug-loading capacity and boost the efficiency of medications taken in combination. In this aspect, nanocapsules are crucial to current drug delivery because they can preserve the medication and have a high drug-loading capacity, increasing the likelihood that the drug will reach the brain. Additionally, the reticuloendothelial system's macrophages are protected from drug detection by these nanoparticles [29].

Nanoparticles in the treatment of central nervous system diseases

Ischemia

A stroke caused by a lack of blood supply to a part of the brain is a neurological disorder. One of the most typical stroke symptoms is the generation of free radicals [30]. Some nanoparticles have the potential to inhibit reactive oxygen species in stroke. Nanoparticles of platinum and cerium oxide, due to their antioxidant properties, have been promising answers for improving and treating stroke. These nanoparticles mimic the activity of antioxidant enzymes and destroy free radicals [31]. The use of these nanoparticles significantly reduces the volume of the damaged area. The use of gold nanoparticles in the treatment of stroke depends on the size of the nanoparticles. A study showed that gold nanoparticles with a size of 20 nm reduced the volume of the damaged area, while the same nanoparticles with a size of 5 nm can cause damage to nucleic acids by accumulating in the nucleus, so the antioxidant property depends on the size of the nanoparticles. Also, in another study, it was shown that cerium oxide nanoparticles reduced the death of rats by reducing the induction of nitric oxide synthesis in the hippocampus of rats [32].Research has shown that the use of nanoparticles causes the neutrophils that cause the immune response to be inhibited and prevent severe brain damage in brain models [33].

Increased nestin protein is effective in post-injury repair mechanisms. Also, this protein is expressed in large amounts during the early stages of development of the central and peripheral nervous system [34]. Researchers showed an increase in the number of cells expressing Nestin as a result of treatment with silver nanoparticles in mouse models of stroke, which indicated the effectiveness of these nanoparticles in neurogenesis [35].

Alzheimer

Alzheimer's disease (AD) or amnestic disease is a type of brain disorder with a gradual weakening in which the functions and mental abilities of the patient are degraded. In Alzheimer's disease, a recent event usually occurs first, and unfortunately, a cause or a suitable treatment is not available.

Accumulated evidence supports the hypothesis that oxidative stress produced by different mechanisms may be among the main factors promoting neurodegeneration [36].

The accumulation of amyloid plaques is one of the known causes of Alzheimer's disease, which is found in all parts of the brain of these patients, and in laboratory environments, beta-amyloid is used to induce Alzheimer's disease in mice. In their research, D'Angelo et al. found that treatment with cerium oxide nanoparticles protects brain neurons against oxidative stress induced by beta-amyloid. The obtained results emphasized the neurotrophic role of these nanoparticles as a factor that can modulate the important pathways of nerve cell survival. Also, Das et al. investigated the antioxidant and neuroprotective properties of cerium oxide nanoparticles in spinal cord injuries. In this research, it was observed that treatment with this nanoparticle causes the growth and survival of nerve cells in the spinal cord [37].

Among the factors of accumulation of amyloid beta proteins, we can mention metal ions such as copper and iron, which increase with age in the brain. Nanoparticles can remove metals from the body or prevent their undesirable functions through their specific bonds. Nanogels have been considered due to their high stability, ability to respond to external stimuli, and high and accurate loading of active substances such as drugs. In Alzheimer's disease, nanogels are also used to prevent the accumulation of amyloid beta plaques [34]. In research that investigated the effects of silver nanoparticles on Alzheimer's disease, the results showed that the surfaces of silver nanoparticles can act as a nano chaperone and inhibit the formation of amyloid fibers. As a result, the medicinal use of these nanoparticles can be useful for the treatment of Alzheimer's disease. Dowding J and his colleagues showed that cerium oxide nanoparticles can switch between their Ce3+ and Ce4+ states and in this way can destroy superoxide anions and hydrogen peroxide. Also, these nanoparticles accumulate in the outer membrane of the mitochondria and prevent the collapse of the mitochondrial structure due to the toxicity caused by beta-amyloid. Therefore, cerium oxide nanoparticles have antioxidant properties, and drug treatment by this nanoparticle can prevent the destruction and death of nerve cells in Alzheimer's disease [38].

Parkinson

Parkinson's disease (PD) mainly affects brain dopaminergic cells. Parkinson's disease is a multifactorial cascade of destructive factors that usually affects people over 65 years old. Loss of dopaminergic neurons leads to tremors, speech, and memory impairment. A subset of patients appears to follow an autosomal dominant inheritance pattern, although in most cases the inheritance pattern is not discernible [39]. Researchers used a method based on nanoparticles to prevent neurodegeneration in animal models of Parkinson's disease to transfer plasmids containing desired genes to the brain. This approach discovered a gene therapy-based method for the treatment of Parkinson's disease that had the potential to repair defective genes [40].

Iron oxide nanoparticles, by affecting the interaction of neurons and surrounding cells, play a significant role in increasing the regeneration capacity of neurons after spinal cord injury. The ability of magnetic iron oxide nanoparticles to track the migration of leukocytes and track cells inside the body can be useful in the study of central nervous system lesions such as Parkinson's, stroke, brain tumors, epilepsy, and Alzheimer's. Stressed or disabled neurons need more energy to survive and repair and improve their function. Improving the metabolic pathways and improving the level of adenosine triphosphate (ATP) (Adenosine triphosphate; and Nicotinamide adenine dinucleotide; NADH)) is one of the characteristics of nanoparticles in the brain [41]. For example, introducing a suspension containing gold nanoparticles into the body of rats has been effective in improving the symptoms of Alzheimer's and Parkinson's disease [42].

Multiple sclerosis

Although the cause of multiple sclerosis (MS) is unknown, it seems to be caused by the interaction of genes and the environment, and diet, sunlight, infections, and genetics are important factors in MS patients. Despite promising advances in the understanding of modern diseases, precise details about the inflammatory processes are still not available [43]. MS is an inflammatory disease that destroys the central nervous system, especially in adults, which causes numbness and vision loss. In early definitions, MS was described as a disease characterized by inflammation around blood vessels and damage to myelin. This disease has been identified in more than 2 million people worldwide, mainly based on medical history and clinical examination of the patient [44].

Obstruction of blood flow in narrow vessels and increased production and accumulation of reactive oxygen species in MS lead to the activation of macrophages and apoptosis in oligodendrocytes [45]. The use of nanoliposomes in modern drug delivery systems, along with their structural similarity to biological membranes, can show fewer side effects and better treatment processes in the target tissue with controlled release and accurate targeting. In research, the use of nanocarriers such as nanoliposomes has shown promising results in improving MS symptoms [46].

For the purpose of describing autoimmune illness in humans and understanding MS, Eitan and his colleagues used mouse models to show the impact of cerium oxide nanoparticles. Clinical symptoms, damage to the white matter of the central nervous system, and inflammation of the central nervous system were all decreased by drug therapy using nanoparticles [47].

Nanoparticles in the treatment of peripheral nervous system diseasesConsidering that different mechanisms are involved in the repair of peripheral nerves, as a result, various molecular signals can be effective in these processes. These signals can play a role in these complex processes separately or in cooperation with each other using specific methods such as a specific expression or deletion of genes in nerve tissue cells or using specific antibodies. Several factors can cause damage to peripheral nerves, in addition to causing changes in the axon of damaged neurons, damage to peripheral nerves can also cause dysfunction of the organs associated with them [48].

As a consequence of the nanoparticles' tiny size, which increases their surface-to-volume ratio and allows them to absorb more free radicals, they may be an effective technique to deal with free radicals produced as a result of nerve injury. It should be emphasized that because such modeling in mice is reasonably affordable, peripheral nerve researchers frequently employ the sciatic nerve as a study tool for nerve healing using varied dosages [49].

The effects of cerium oxide nanoparticles on enhancing motor function and tissue alterations after sciatic nerve damage in rats were studied by Soluki et al. When compared to the control group, the groups that received cerium oxide treatment recovered considerably faster and had improved motor function. Additionally, it was shown that cerium oxide nanoparticles decreased cell apoptosis and were successful in peripheral nerve healing in a study that examined the effects of oxidative stress on endothelial cells and nerve cells. Reducing oxidative damage also increases the lifespan of neuron cells, and because cerium oxide has antioxidant properties, cerium oxide nanoparticles can swiftly act and absorb reactive oxygen species during this process. Additionally, this chemical has been shown to have impacts on angiogenesis, nervous system modulation, anti-cancer applications, decreasing high blood pressure, antimicrobial properties, lowering cholesterol levels, and preventing damage to injured tissue [11].

There is a lot of optimism for developing medical diagnostic and therapeutic facilities thanks to the characteristics of nanoparticles. Magnetic nanoparticles are a popular molecule for diagnostic and therapeutic applications because they may deliver medications to desired areas using a magnetic field [50].

Scientists are trying to repair nerves by optimizing the properties of nanoparticles and stimulation

parameters.

Gold nanoparticles, as a substrate and matrix that is electrically conductive, are a promising material for the regeneration of peripheral nerves [42]. In diseases of the nervous system, it is also possible to disperse drug particles in a very small size in an external liquid phase using nanosuspensions. Ease of manufacturing process, much lower toxicity, and increased efficiency are the advantages of nanosuspensions [18]. Nanocarbon formulation can also be used for various applications such as cancer diagnosis, imaging drug delivery, and tissue engineering [51].

CONCLUSION

Following damage to the nervous system, the use of neuroprotective agents is a suitable strategy to control the damage and restore the system. Nowadays, the use of nanoparticles as a new factor has been widely considered. Some nanoparticles have neuroprotective properties due to their antioxidant properties and other chemical and morphological characteristics. In general, nanoparticles are promising therapeutic methods that are still in the early stages, but considering extensive studies in this field, this therapeutic approach is expected to be one of the useful therapeutic agents in the treatment of neurological lesions in the future.

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