Panacea Journal of Pharmacy and Pharmaceutical Sciences

http://internationaljournal.org.in/journal/index.php/pjpps/index

ISSN: 2349-7025

SPECIAL THEMATIC ISSUE APRIL-JUNE 2018

VOLUME 7 ISSUE 2

Part II

INDIAN PHARMACEUTICAL ASSOCIATION

"Building India into a Pharma Superpower (2020)"

MEET: APRIL 2018

Panacea Journal of Pharmacy and Pharmaceutical Sciences 2018:7(2);055-101
International Journal ISSN: 2349 7025

PHARMACOPHORE MAPPING AND MOLECULAR DOCKING OF FLAVONES AS RAF INHIBITORS; AN ANTI-CANCER APPROACH

Kapish Kapoor[1*], Naveen Dhingra [2], Brij Patel[3]

[1]School of Pharmacy, Devi Ahilya University, Takshshila Campus, Khandwa Road, Indore-452001, M.P., India
[2]Institute of Science, SAGE University, Kailod Kartal, Indore-452020, M.P., India
[3]Sullivan University, Gardiner lane, Louisville-40205, Kentucky, U. S. A.

E-mail: kapish11.kk@gmail.com

ABSTRACT

Cancer is one of the leading causes of deaths around a globe, every year millions of patients die due to this disease. RAF The receptor tyrosine kinase effector, named for Rapidly Accelerated Fibrosarcoma, There are three known mammalian Raf isoforms: A, B andC-Raf, we took 200 flavones derivatives from pubChem and virtual screening was done for the identification of the compounds. Molecular Docking was performed on Molegro Virtual Docker 6.0 on the PDB: 5C9C. The docking results revealed that compound FL-119 showed active inhibition of the RAF isoforms, further pharmacophore mapping was done for the identification of the compound for the detection of H-donors, H-acceptors and Steric interactions. Lipinski rule was applied for top 10 compounds. The mol dock score was found to be-159.483 the rerank score was found to be-123.502 and the H-bond score was found to be-12.1337. The study showed that the most active compound FL-119 bind to the active site of the protein with amino acids Lys-482. This study suggests that these compounds can be further used for the designing of novel drug in treatment of cancer.

KEYWORDS: RAF isoforms, cancer, docking

OBJECTIVE

The objective behind the study was to design a potent and a therapeutically active drug for the treatment of cancer, which act as a inhibitor of Raf isoforms which are responsible for cancer.

EXPERIMENTAL

Molecular Docking: Molecular docking was performed on transferase inhibitor BRAF(V600E); (PDB code: 5C9C) retrieved from protein data bank in Molegro Virtual Docker ver. 6.0. Active amino acids according to the literature which forms hydrogen bonds are Lys482, Asp593, Glu500, Cys531 and further pharmcophore mapping was done.

Lipinski Rule: Lipinski rule were followed for the best docked compounds.

RESULT AND DISCUSSION

Molecular Docking: Molecular docking result revealed that the most active compound FL-119 bind to the active site of the ligand. It binds to the active amino acid Lys-482 with similar distance as of ligand incorporated in the protein, The MolDock score was found to be-159.438 and Re-rank score was found to be-123.502 for the compound.

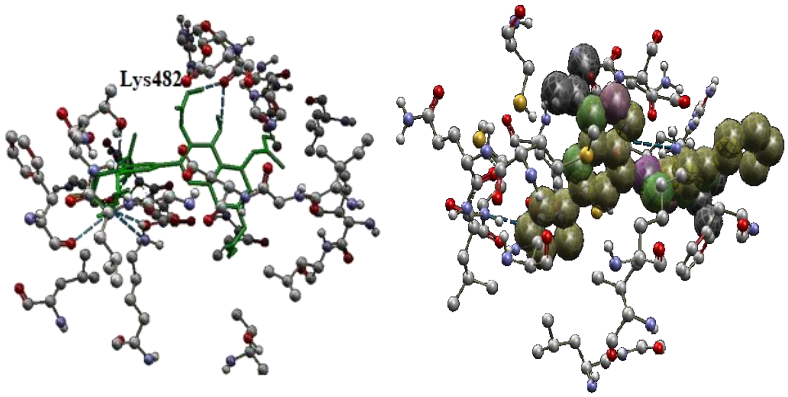

Figure 1. (a) H-bond interactions of FL-119 with protein and (b) pharmacophore mapping done on FL-119

Table 1: Results obtained by pharmacophore mapping

H-Acceptors	**8**
H-Donors	**4**
Steric Interactions	**50**

CONCLUSION

The given study is valuable, inexpensive and important for further *in vitro* and *in vivo* studies. Selected Flavones analogues can be studied for their therapeutic potential in treating cancer.

ACKNOWLEDGMENTS

I would like to thank Prof. Rajesh Sharma Head, School of Pharmacy, DAVV, Indore for providing the facility for the work. I would also like to thank Dr. Naveen Dhingra for guidance on this topic.

REFERENCE

1. Application of descriptors based on Lipinski's rules in the QSPR study of aqueous solubilities Pablo R. Duchowicz,a,* Alan Talevi,a,b Carolina Bellera,b Luis E. Bruno-Blanchb and Eduardo A. Castroa.
2. Alavi A, Hood JD, Frausto R, Stupack DG, Cheresh DA. (2003). Role of Raf in vascular protection from distinct apoptotic stimuli. *Science* 301: 94–96.
3. New therapeutic aspects of flavones: The anticancer properties of *Scutellaria* and its main active constituents Wogonin, Baicalein and Baicalin Author links open overlay panel MinLi-Weber, Cancer Treatment ReviewsVolume 35, Issue 1, February 2009, Pages 57-68.

TETANUS-A NEED FOR A LONG TERM VACCINE

Kshitij Chitnis, Deeksha Rajput, Nayan Shroff

School of Pharmacy, Devi Ahilya University, Takshshila Campus, Khandwa Road, Indore-452001, M.P., India

ABSTARCT

Tetanus, also called lockjaw, is an infection caused by a bacterium *Clostridium tetani.* When *Clostridium tetani* enters the body through contaminated soil they multiply rapidly and release tetanospasmin, a neurotoxin. When tetanospasmin enters the bloodstream, it rapidly spreads around the body, and interferes with the signals traveling from the brain to the nerves in the spinal cord, and then on to the muscles, causing severe muscle spasms, serious breathing difficulties, and can ultimately be fatal in about 30% cases.

The effective vaccine is TETANUS TOXOID which is prepared by using a highly toxigenic strain of *Clostridium tetani*. These antigens are given in subcutaneous manner and involve whole immune system, termed T-dependent vaccines since the involvement of T helper cells is essential for the immune response generated.

The invention of vaccination was a turning point in the war between microbes and humans. But one has to take TT shots after every 6 mo as Toxoids have short life span. This is a painful process. An attempt is being made to understand the mechanism of T and B cells involved and to formulate a dose that can be given as a single shot for the lifelong protection.

KEYWORDS: Tetanus, Vaccine, Tetanus Toxoid

INTRODUCTION

Tetanus is a familiar disease and so is its vaccine. It was a major lethal disease of humans until recently. This is a non communicable disease. It is caused by a bacterium *Clostridium tetani* which is ubiquitously present in soil, on rusted articles. Bacteria of tetanus enter through a punctured wound, dead tissue and/or umbilical cord. The bacterium multiplies in these wounds and release two neurotoxins tetanospasmin and tetenolysin. When tetanospasmin enters

the bloodstream, it rapidly spreads around the body, and interferes with the signals traveling from the brain to the nerves in the spinal cord, and then on to the muscles. Muscles throughout the body are affected, including the vital muscles necessary for normal breathing. It causes the muscles to tighten up into a continuous ("tetanic" or "tonic") contraction or spasm. The jaw of patient is "locked" by muscle spasms, giving the name "lockjaw" (also called "trismus"). When the breathing muscles lose their power, breathing becomes difficult or impossible and death can occur in about 30% cases.

The first vaccine for passive immunology was discovered by a group of German scientists under the leadership of Emil von Behring in 1890. The tetanus vaccine was developed in 1924 and became available in the United States in the 1940s. Its production was boosted during World War II when it was used in wounded soldiers and saved thousands of lives. After World War II, its application in pregnant ladies saved millions of newborns to get succumbed to jaws of death. Its use resulted in a 95% decrease in the rate of tetanus related deaths.

METHOD OF ACTION

Once the bacteria *C. tetani* enters the body the spores multiply and germinate due to the anaerobic environment. and two toxins are released: tetanospasmin and tetenolysin.[4] It is not certain the exact role of tetanolysin but it is believed that it works together with the toxin tetanospasmin.[4] Tetanospasmin reaches the peripheral nerves by retrograde neuronal transport through the blood or lymphatic system.[4] "The length of the peripheral nerves determines how long it takes for the neurotoxins to reach the CNS and cause symptoms. The toxin tetanospasmin disrupts the release of the inhibitory neurotransmitters glycine and GABA throughout the CNS but most commonly at the motor end plates, spinal cord, brain, and sympathetic nervous system".[2] "The inhibition allows for unopposed muscular contraction followed by muscular rigidity and spasms".[4] Once the bacteria have entered the body the incubation period may range from days to months but the average is around 4-14 d. As a result a person experiences uncontrollable intense muscle contractions.[4] The first muscles affected are the facial and jaw muscles because of their short nerve pathways. Spasms can be produced by a stimulus such as light, noise, touch, or happen unexpectedly with no specific cause.[4] Spasms are extremely painful and can occur frequently and can last for several minutes.[4]

Tetanus toxoid vaccine is manufactured by growing a highly toxigenic strain of *Clostridium tetani* in a semi-synthetic medium: bacterial growth and subsequent lysis release the toxin into the supernatant and formaldehyde treatment converts the toxin to a toxoid by altering particular amino acids and inducing minor molecular conformational changes. Ultrafiltration then removes unnecessary proteins left as a residual from the manufacturing process to produce the final product. The toxoid is physico-chemically similar to the native toxin thus inducing cross-reacting antibodies but the changes induced by formaldehyde treatment render it non-toxigenic [4].

When this toxoid is administered subcutaneously they are taken up by immature dendritic cells and bound to major histocompatibility complex type II (MHC II) molecules; the MHC II: toxoid complex then migrates to the cell surface. where they encounter naive T helper type 2 cells (T_H2), each with their own unique T-cell receptor (TCR). Identifying and then binding of the MHC II: toxoid to the specific T_H2 receptor then activates the naive T cell, causing it to proliferate. Simultaneously, toxoid molecules not taken up by dendritic cells pass along lymph channels to the same draining lymph nodes where they come into contact with B cells, each with their own unique B-cell receptor (BCR).

This mechanism depends on the T cells so this vaccine is known as T-dependent vaccines since the involvement of T helper cells is essential for the immune response generated. The tetanus vaccination acts by generating antibodies against the toxoid which have an enhanced ability to bind toxin compared with the toxin receptor binding sites on nerve cells; in the event of exposure to *C. tetani*, this large toxin: antibody complex is then unable to bind to the receptor so neutralizing the toxin and preventing disease development.

Toxoid vaccines have some advantages as-They are safe, They do not spread in unimmunized individuals, they are usually stable and long lasting. Toxoid vaccines have some disadvantages also

- it is a toxoid
- it need an adjuvant
- It can't replicate itself
- It has to be given in repeated dose.
- local reactions at the vaccine site are more common

- People are sometimes allergenic to this

CONCLUSION

Dr. Pål Stenmark's team has determined the three-dimensional structure of the entire tetanus toxin protein. We can now see the exact positions of the 20 000 atoms that build up the tetanus toxin. Structure of toxoid protein is also similar to the structure of toxin protein. It means that we can see how both the toxin and vaccine actually look.

As toxoids show a fall in serum level after six months and we have to give fresh shot of toxoids in case of adults and children have to be immunized after every 10 y.

If we make necessary amendments in the toxin so that it can induce antibody production in a limited and steady manner it can directly be used as vaccine. This will give a better serum level of antigen for a longer period.

The protein has different structures at different pH. This property can also be used for vaccine preparation.

This is a preliminary thought to develop an alternative vaccine. Available vaccine is an effective vaccine which has eradicated tetanus in many countries and has successfully saved life of enumerable persons. The only drawback of this is being its shorter life span.

Through this innovation an attempt is being made to lessen the piercings.

REFERENCES

1. Baxter D. *Occupational Medicine*, Volume 57, Issue 8, 1 December 2007, Pages 552–556
2. Stenmark P. 3-d structure of tetanus toxin reveals a shape shifter. Posted on June 30, 2017 by scientificinquirer
3. Wakim N, Henderson S. Tetanus. Topics in Emergency Medicine. July 2003;25(3):256-261.
4. Cook T, Protheroe R, Handel J. Tetanus: a review of the literature. British Journal Of Anaesthesia. September 2001;87(3):477-487. Available from: MEDLINE, Ipswich, MA. Accessed April 2, 2011.

WOUND HEALING ACTIVITY OF THE HYDRO-ALCOHOLIC EXTRACT OF *CAPSICUM ANNUM FRUITS* IN WISTAR ALBINO RATS

Shekhar Priyanshu*, Joshi Ankur, Malviya Sapna and Kharia Anil

Modern institute of Pharmaceutical Sciences, Indore-453111, M. P., India

E-mail: priyanshupatna011@gmail.com

ABSTRACT

A cut, blow, or other impact, typically one in which the skin is cut or broken living tissue caused an injury. Due to side effects and cost effectiveness treatments are limited. In this, we attempted to use a natural source to study its potential towards the wound healing process. Therefore, *Capsicum annum,* an edible and medicinal plant, was chosen as the target sample for the study. During this investigation, the wound closure properties using fruit extract of *Capsicum annum* were analyzed. *Capsicum annum* fruits were dried, crushed in coarse powder hydro-alcoholic extract was obtained and turned to 10% ointment form. In the course of this study, 18 albino rats weighing approximately 150-180g were used in this research. Group 1 as control group, Group 2 as reference control were treated topically with gentamicin ointment, Group 3 as test control were treated with 10% *Capsicum annum* ointment. Wound healing was monitored on days 4, 8, 12, 16. This study suggested that the fruit extract of *Capsicum annum* have a potential therapeutic agent for skin wound healing, supporting its traditional medicinal uses.

KEY WORDS: Wound healing; *Capsicum annum* (fruits); hydro-alcoholic extract; ointment; bactericidal activity.

INTRODUCTION

Wound is a full or partial interruption in the integrity of the skin, there are various drugs obtained from plant source are known to increase the healing of different types of wounds. For standard healthcare herbal medicines has integral part, based on a combination of time honored traditional uses and ongoing scientific research. The fruits and routes

contains tannins (argimonin and pedunculagin), Vitamin C, traces of oil, flavonoids (quercetin and rutin), phenolic acid. The objective of present study is to compare the effect of *Capsicum annum* fruits (Shimla Mirch) and Gentamicine sulphate ointment, in terms of size of the wound until full *epithelialization* and the progress of the wound until final healing.

EXPERIMENTAL

Animals

18 male Wistar rats (150-200g) were divided into three groups of six rats. The animals were housed in standard environmental condition. During the course of the experiment the rats were administered a standard pellet diet and water *adlibitum*.

Surgical procedure

The rats was anesthetized by thiopental sodium and then fixed in a ventral posture on a surgery table anesthesia was given in the depth of muscle, avoiding incision of the muscle layer itself and tension of skin was kept constant during the procedure. An area of uniform wound 2 cm in diameter was excised from the neck.

Treatments

After making the surgical wounds, all rats were randomly divided in three different groups.

Group I: control
Group II: was dressed using the Gentamicine sulphate Ointment
Group III: was dressed using the *Capsicum annum* (fruits)ointment.

On day five, ten and fifteen, and twenty one four animals were randomly selected for observation of percentage of healing of wound on the rats.

Wound size at day zero (0)–Wound size on the given day X 100

Results and Discussion

The effect of hydro alcoholic fruit extract ointment on excision wound model, the wound healing contracting ability in different contraction was significantly greater than that of control. The 10%w/w extract ointment treated groups showed significantly wound healing from fourth day onwards, which was comparable to that of the standard drug, Gentamicin Ointment treated groups of animals. Closure time of the wound was lesser, and the wound contraction percentage was much more with the 10% w/w extract ointment treatment group. The result of present study revealed that hydro-alcoholic extract of *Capcicum annum* fruits have significant wound healing activity in both incision as well as excision wound model.

Table 1. Effect of Hydroalcholic extract ointment of fruits of *Capsicum annum* on % wound closure of excision wounds

Group	Treatment	5th Day	10th Day	15th Day	21st Day	Period of epithelization in days
Group I	Control (Simple ointment base B. P.)	15.82±0.68	27.21±1.02	48.21±1.80	68.53±2.60	26
Group II	Gentamicine sulphate Ointment	35.28±0.15	76.80±0.19	89.81±0.58	97.11±0.48	1
Group III	Hydroalcholic extract (10%)	34.42±1.01	76.86±1.24	84.32±2.36	92.56±2.10	17*

CONCLUSION

In this study, the effect of *Capsicum annum* fruits was screened for wound healing activity on adult male wistar rats. This research has therefore showed that *Capsicum annum* has agents to promote wound healing activity.

REFERENCES

1. Patil S, Ghodke D S Magdum C S et al. Evaluation of healing activity of marketed formulations on excision wounds models in Albino rats Int J Pharm Tech Res 2009; 1: 500–501.
2. Chitra P, Sajithal G B, Chanrakaran G. Influence of Aloe Vera on collagen turnover in healing of dermal wounds in rats. Ind J Exp Biol 1998; 36: 896–901.
3. Pandey M, Worlikar P S et al. Comparison of wound healing activity of Jethimadh with Triphala in rats. Int J Health and Allied Sciences 2012; 1: 59–63.

ANALGESIC ACTIVITY OF HYDRO ALCOHOLIC EXTRACT OF *ZIZYPHUS JUJUBA* LEAVES

Sirvi Someshver*, Joshi Ankur, Malviya Sapna and Kharia Anil

Modern Institute of Pharmaceutical Sciences, Sanwer Road, Indore-453111, M.P.

E-mail: jaysirvi87@gmail.com

ABSTRACT

The aim of the present investigation is to evaluate the analgesic activity of hydro alcoholic extract of *zizyphus jujuba* leaves on wister albino rat. Analgesic activity of the hydro alcoholic extract of the *zizyphus jujuba* at a dose of 100 mg/kg and 200 mg/kg was evaluated against the standard drug Pentazocine at a dose of 10 mg/kg. Adult wister albino rat of either sex of divided in to 4 groups comprising six numbers in each group was undertaken for study and evaluated by hot plate method and tail flick method. The two doses of hydro alcoholic extract of *zizyphus jujuba* leaves was found to produce significant ($p<0.05$ and $p<0.01$) analgesic activity. In tail flick method, the crude extract produced elongation of time 30 min after oral dose of 100 and 200 mg/kg body weight respectively. Test drug at a dose of 200 mg showed better analgesic activity in comparison to 100 mg dose by both the methods. So, it can be recommended for further studies.

KEYWORDS: Analgesic, Zizyphus Jujuba, Pentazocine, hydro alcoholic extract

INTRODUCTION

Pain is the part of a protective reaction against dysfunction of an organ or imbalance in its functions against potentially dangerous stimulus. It is an unpleasant feeling often associated with tissue damage. The drugs that selectively relieve pain by acting on the CNS are called as analgesics. It also acts on peripheral pain mechanisms, without significantly altering consciousness. Analgesic relieves pain as a symptom not cure the cause of pain. Analgesics are of two type opioid analgesic or non-opioid analgesic. In recent times, focus on plant research has increase. Herbal drugs are being proved as effective as synthetic drugs with lesser side effects. Herbal medicines are in line with nature, with less hazardous reaction. The use of herbal medicines worldwide has provided a great opportunity to India to look for therapeutic conduct compounds from our oldster system of therapy, i.e. Ayurveda, which can be utilized for development of new drug.

MATERIALS AND METHODS

Experimental animal

Wister albino rats weighing 150-200g were housed in standard cages at room temperature 22±2 °C and 50±5% relative humidity, under a light/dark cycle of 10/12 h, for 1 w before the experiments. Animals were provided with standard rodent pellet diet (Indore, India), and water *adlibitum*.

Evaluation of Analgesic Activity

Hot Plate Method

The analgesic activity of the given drug was determined by the basal reaction time. A total of 24 rat of either sex were divided into four groups. Group I was kept as control, administered with distilled water (10 ml/kg) and Group II was treated with standard drug Pentazocine (10 mg/kg). Group III and IV were treated with two different concentrations of hydro alcoholic extract of Zizyphus Jujuba (100 mg/kg and 200 mg/kg body weight) orally 30 min prior to the start of the experiment. The heated hot plate, maintained at 55±0.5˚C was used to induce pain. Before the treatment, the reaction time of each animal (paw licking or jumping) was recorded. The reaction time was recorded at 1, 2, 3 and 4 h following the administration of Ethnolic extract of Zizyphus jujuba and Pentazocine. In order to minimize damage to the animal paw, the cut off time for latency was taken as 25 sec.

Tail flick Method

Wister rat were screened for sensitivity test by placing the tip of the tail on the radiant heat source. Any animal that failed to withdraw its tail within 5 s was rejected from the study. The selected animals were then divided into four groups of six rats each. Each of the groups received one of the following: extract (100 and 200 mg/kg), Pentazocine (standard, 10 mg/kg) and distilled water (control) in normal saline intraperitoneally. Basal reaction time was measured initially (0 min) and at 15, 30, 45 and 60 min. A cut-off period of 10 sec was observed to avoid damage to the tail

RESULT

Analgesic activity

The analgesic activity was performed by Hot plate method and Tail flick method which shows dose dependent pain inhibition with ethanol extract as mentioned in (table 1 and 2).

$$\text{Percentage pain inhibition} = \frac{\text{control reading} - \text{test reading}}{\text{control reading}} \times 100$$

Table 1. Analgesic activity of hydro alcoholic extract of *Zizyphus Jujuba* in Eddy's hot plate method.

Group	Treatment	Dose	0 min	30 min	60 min	120 min	180 min
I	Control	1 ml/kg	16.2	16.4	17.3	16.1	16.0
II	Pentazocine	10 mg/kg	18.25	43.38	48.5	47.3	42.4
III	Lycium barbarum extract	200 mg/kg	20.54	25.67	28.4	30.45	27.86
IV	Lycium barbarum extract	400 mg/kg	22.91	28.37	33.54	39.67	35.57

Table 2. Analgesic activity of hydro alcoholic extract of *Zizyphus Jujuba* in Tail flick method.

Group	Treatment	Dose	0 min	15 min	30 min	45 min	60 min
I	Control	1 ml/kg	2.41	2.47	2.49	2.64	2.75
II	Pentazocine	10 mg/kg	2.21	8.9	11.54	14.74	17.45
III	Lyceum barbarum extract	200 mg/kg	2.45	5.45	7.14	8.74	9.23
IV	Lyceum barbarum extract	400 mg/kg	2.98	6.54	8.44	10.7	12.6

CONCLUSION

The present experimental study protocol showed that hydro alcoholic extract of Zizyphus Jujuba elicited significant analgesic activity in Eddy's hot plate model and tail flick latency model. In both model they exhibited analgesic effect in

a dose dependent manner which can be comparable with that of Pentazocine. On preliminary phytochemical screening the hydro alcoholic extract of Zizyphus Jujuba was found to contain Sterols and Triterpenes compounds.

REFERENCES

1. Goyal B, *Et al.*, Evaluation of analgesic activity on ethanolic extract of *Tamarindus indica* leaves. International Journal of Pharmaceutical Sciences and Research 2013; P. 1995.
2. Ukwuani A. N, Analgesic properties of *Tamarindus indica* linn stem bark fractions in albino rats, sky journal of biochemistry 2014;24-27.
3. Kumari P, synergistic analgesic activity of chloroform extract of lawsonia inermis linn. And chlorophytum borivilianum, journal of pharmacognosy and phytochemistry 2015;35-38.

RETROPERITONEAL FIBROSIS

Soumya Mishra, Hinal Shah, Kriti Shrivastava, Ashwini Dashore

School of Pharmacy, Devi Ahilya University, Khandwa Road Indore-452001, M.P., India

E-mail: soumyamishra2929@gmail.com

INTRODUCTION

Retroperitoneal fibrosis is a rare disease in which excess formation of connective tissue [fibrosis] take place behind the stomach and intestine [retroperitoneal area]. The excess tissue mass often results in hindrance of tubes that carry urine from kidney to the bladder [ureters]. Due to blockage of ureter, urine rearwards in ureter which contain injurious material that can damage kidney and if not treated it can lead to kidney failure.

Abdominal aorta is the location from which problem generally begins. Abdominal aorta supplies blood to abdominal and pelvic organs and legs.

SYMPTOMS

a. Mainly the symptom includes dull pain in lower abdomen, back, and scrotum.
b. Anemia which can also cause pain and discoloration of leg due to reduced blood flow.
c. There may be bleeding and hemorrhaging in abdomen.
d. Fever, weight loss, appetite loss, nausea,vomiting
e. Anorexia
f. Malaise
g. Lower extremity edema
h. Deep venous thrombosis
i. Phlebitis
j. Inability to urinate with decreased urine production.
k. Impaired physical mobility
l. Unable to think clearly.
m. Accumulation of urine may result in the kidney failure.

One should consult the doctor when it have abdomen pain with reduced urine output.

CAUSES AND RISK FACTOR

The close cause of retroperitoneal fibrosis is idiopathic [not known] in about two-thirds of the affected individuals. Age and gender are the major risk factor of disease. More males are affected than female. According to the National Center for Biotechnology Information, it occurs most often between the ages of 40 and 60. The problem is associated with the use of some medications to treat high blood pressure and medications to treat migraines called ergotamine.

DIAGNOSIS

Diagnosis can be done by ultrasonography however the accurate diagnosis includes use of CT or MRI scans of your abdomen.

Other test include-

- Erythrocyte sedimentation rate level
- C-reactive protein level
- Urea and creatinine levels
- Complete blood count: Normocytic normochromic anemia
- Alkaline phosphates levels
- blood tests to measure kidney function, anemia, and inflammation
- an X-ray of the kidneys and ureter

TEREATMENT

If the disease is in early stages the immunosuppressant's [e. g., mycophenolate, azathioprine], corticosteroid [e. g., prednisolone, prednisone] and anti-inflammatory medicines can work upon but if the disease has started affecting the ureters by blocking one or both the ureter then Surgery is often done on organ on constricted organ. In some cases, stents may be implanted within the ureter to provide temporary relief from obstruction. Stent is inserted through back into kidney. A stent may also be run from bladder through the ureter into the kidney.

The goal of surgery is to remove the blockage from tissue, repair the affected area and prevent it from further regrowth of fibrosis.

PREVENTION

As the cause of disease is idiopathic prevention may not be possible but as the condition is linked with the use of medications used in high blood pressure and migraine known as erigotamines. So we should know the side effects of medicine avoid that medicine or have an alternative of that medicine.

CONCLUSION

The complication of disease is different in cases in which the size and place of the excess tissue growth can lead to damage of various areas served by the abdominal aorta.

If the condition is diagnosed and treated at an early stage, the recovery of patient is very good. When kidney damage is minimal and surgery is successful, there's a 90 % chance of long-term success.

However, in cases where the kidneys damage is more, damage can be permanent which results in kidney transplant.

REFRENCES

1. Amis, E. S. (1991, August). Retroperitoneal fibrosis. American Journal of Roentgenology, 157(2), 321-329 ajronline. org/content/157/2/321. long
2. Idiopathic retroperitoneal fibrosis. (n. d.) urology. med. nyu. edu/conditions-we-treat/conditions/idiopathic-retroperitoneal-fibrosis
3. Retroperitoneal fibrosis. (2011, March 17) ncbi. nlm. nih. gov/pubmedhealth/PMH0001497/
4. Genetic and Rare Diseases (GARD) Information Center
5. National Kidney Foundation
6. NIH/National Institute of Diabetes, Digestive and Kidney Diseases
7. Retroperitoneal fibrosis. (2008, May 5) rarediseases. org/rare-disease-information/rare-diseases/byID/849/viewFullReport
8. Retroperitoneal fibrosis. (2008, September 24) rarediseases. info. nih. gov/GARD/Condition/9568/Retroperitoneal_fibrosis. aspx
9. Scheel, P. (n. d.). Retroperitoneal fibrosis hopkinsmedicine. org/nephrology/retroperitoneal_fibrosis. html

Panacea Journal of Pharmacy and Pharmaceutical Sciences 2018:7(2);055-101
International Journal ISSN: 2349 7025

ANTIULCER ACTIVITY OF FEW INDIAN MEDICINAL PLANTS: A REVIEW

Jain Deepali*, Joshi Ankur, Malviya Sapna, Kharia Anil

Modern Institute of Pharmaceutical Sciences, Indore, M.P., India

E-mail: deepalijainbio@gmail. com

ABSTRACT

Among many people ulcer is a common gastrointestinal disorder is seen. It is basically an inflamed break in the skin or the mucus membrane lining the alimentary tract. Ulceration occurs when there is a disturbance of the normal equilibrium caused by either enhanced aggression or diminished mucosal resistance. It may be due to the regular usage of drugs, irregular food habits, stress, and so forth. Peptic ulcers are a broad term that includes ulcers of digestive tract in the stomach or the duodenum. Due to the presence of acid and peptic activity in gastric juice plus a breakdown in mucosal defenses formation of peptic ulcers occurs. A number of synthetic drugs are available to treat ulcers. But these drugs are expensive and are likely to produce more side effects when compared to herbal medicines. The literature revealed that by various ayurvedic doctors and traditional medicinal practitioners today many medicinal plants and polyherbal formulations are used for the treatment of ulcer. The ideal aims of treatment of peptic ulcer disease are to relieve pain, heal the ulcer, and delay ulcer recurrence. In this review attempts have been made to know about some medicinal plants which may be used in ayurvedic as well as modern science for the treatment or prevention of peptic ulcer.

KEYWORDS: Plant Drug, Alkaloids, antiulcer activity, flavonoids, peptic ulcer, saponin, tannins.

INTRODUCTION

An open sore of the skin or mucus membrane characterized by sloughing of inflamed dead tissue are known as ulcers. They are lesions on the surface of the skin or a mucous membrane caused by a superficial loss of tissue. There are many types of ulcer such as mouth ulcer, esophagus ulcer, peptic ulcer, and genital ulcer. Of these peptic ulcer is seen among many people. The peptic ulcers are erosion of lining of stomach or the duodenum. The two most common types of peptic ulcer are called “gastric ulcer” and “duodenal ulcer.” The name refers to the site of ulceration. A person may have both gastric and duodenal ulcers at the same time. A person may have both gastric and duodenal ulcers at the same time. Gastric ulcers are located in the stomach, characterized by pain; ulcers are common in older age group. Eating may increase pain rather than relieve pain. Other symptoms may include nausea, vomiting, and weight loss. Although patients with gastric ulcers have normal or diminished acid production, yet ulcers may occur even in complete absence of acid. Duodenal ulcers are found at the beginning of small intestine and are characterized by severe pain with burning sensation in upper abdomen that awakens patients from sleep. Generally, pain occurs when the stomach is empty and relieves after eating. Peptic ulcer is one of the world’s major gastrointestinal disorders and affecting 10% of the world population. About 19 out of 20 peptic ulcers are duodenal. An estimated 15000 deaths occur each year as a consequence of peptic ulcer.

INDIAN MEDICINAL PLANTS WITH ANTI-ULCER ACTIVITY

Acacia arabica

Acacia arabica is common all over India in sandy localities. It is commonly known as “babul tree” and locally called as “karuvelam.” Belonging to the family Mimosaceae, Chemical constituents reported in this plant are gum containing arabic acid combined with calcium, magnesium, and potassium and also small quantity of malic acid, sugar, moisture 14%, and ash 3-4%. Bark contains a large quantity of tannin; pods contain about 22.44% tannin.

Adansonia digitata

Adansonia digitata belonging to the family Malvaceae is commonly known as “boabab or monkey-bread tree of Africa.” It is locally known as “paparapuli.” It is one of the largest and long-lived trees in the world, met with chiefly in Bombay, Gujarat, and Coromandal Coast and Ceylon. Chemical constituents in this plant are Pulp that contains phobaphenes, mucilage and gum, glucose, tartrate and acetate of potash, and other salts. A leaf contains wax, glucose, salts, gum, and albuminoids. Bark contains wax, soluble and insoluble tannin, acid gum, albuminous carbonate and chloride of sodium and potassium, and a glucoside adansonin.

Aegle marmelos

Aegle marmelos which is commonly known as a "bael tree" (family Rutaceae) is the plant that chiefly grows on throughout India. It is locally called as "vilvam." Chemical constituents in this plant are flavonoids, tannins, and saponins.

Allium sativum

Allium sativum belonging to the family *Liliacea* is commonly known as "garlic" and also called as "vellapundu." It is cultivated all over India. Arean acrid volatile oil which is the active principle, starch, mucilage, albumen, and sugar are constituents of this plant. Seeds contains aromatic oil. The oil constituents, is rich in sulphur, iodine, and salicylic acid combinations, and complementary substances containing vitamins.

Aloe vera

Aloe vera is of Liliaceae family and is commonly known as "aloe gel." It is also called "kattalai" which is found all over India. Aloin, isobarbaloin, and emodin are some chemical constituents in this plant.

Annona squamosa

Annona squamosal belonging to the family Annonaceae. It is commonly known as "custard apple." It is cultivated in all over India is locally called as "sitapalam." Chemical constituents in this plant Alkaloids, flavonoids, saponins, and tannins are some chemical constituents in this plant. Seeds yield oil and resin.

Azadirachta indica

Azadirachta indica belonging to the family Meliaceae and is cultivated nearly all over India and in Bengal. It is also known as "neem" and locally called "vembu.". Nimbidin, phenolic compounds, saponin, and flavonoid are chemical constituents reported in this plant. It contains a bitter alkaloid named Margosine. Seeds of this plant contain about 10–31% of a yellow bitter fixed oil. The oil contains. volatile fatty acids and small amount of lauric acid.

Bauhinia variegate

Bauhinia variegate (family Caesalpiniaceae) is indigenous to and grow on the Sub-Himalayan tract and the forests of India and Burma. It is commonly known as "orchid tree" and locally called "shemmandarai." Chemical constituents reported in this plant are quercetin, rutin, apigenin, and apigenin 7-0-glucoside. Bark contains tannins, glucose, and a brownish gum.

CONCLUSION

From this study we can conclude that studies with plant sources can result in novel and effective pattern of treatment. Current stalemates of modern medicine in the management of various ailments incline research tendencies to traditional medicine. In this respect, traditional medicine has introduced good protocols for treatment of various gastrointestinal disorders. All of the remedies presented here had adequate evidence from traditional or scientific source for their efficacy in management of ulcers. Chemical substances derived from plants have been used to treat human diseases since the dawn of medicine. Roughly 50% of new chemical entities introduced during the past two decades are from natural products. Recent technological advances have renewed interest in natural products in drug discovery.

REFERENCES

1. F. K. L. Chan and D. Y. Graham, "Review article: prevention of non-steroidal anti-inflammatory drug gastrointestinal complications—review and recommendations based on risk assessment," Alimentary Pharmacology and Therapeutics, vol. 19, no. 10, pp. 1051–1061, 2004.
2. B.Debjit, C. Chiranjib, K. K. Tripathi, Pankaj, and K. P. Sampath Kumar, "Recent trends of treatment and medication peptic ulcerative disorder," International Journal of PharmTech Research, vol. 2, no. 1, pp. 970–980, 2010.
3. N. S. Vyawahare, V. V. Deshmukh, M. R. Godkari, and V. G. Kagathara, "Plants with anti-ulcer activity," Pharmacognosy Review, vol. 3, pp. 108–115, 2009.

Panacea Journal of Pharmacy and Pharmaceutical Sciences 2018:7(2);055-101
International Journal ISSN: 2349 7025

IBUPROFEN USE IN EARLY PREGNANCY MIGHT IMPACT FEMALE OFFSPRING'S FERTILITY

Kriti Shrivastava*, Hinal Shah, Soumya Mishra

School of Pharmacy, Devi Ahilya Vishwavidyalaya, Khandwa Road, Indore-452001, M.P., India

E-mail: suchishrivastava27@gmail.com

ABSTRACT

Analgesics, including paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen, are among the most widely used and environmentally prevalent pharmaceutical drugs in the world. They are regarded as extremely effective medications and self-medication, including by pregnant women during early pregnancy. During pregnancy, a pregnant women also take analgesics in order to get rid of migraine, pain, and fever, but are also used in inflammatory conditions and are frequently used during preterm labor but many evidences and theories indicates that analgesic use in pregnancy can impair the offspring's future reproductive capacity. When we expose our foetus to different range of concentrartion(about 10μM and 100 μM) that resulted in a number of effects indicating impaired ovarian development, including reduced cell number, fewer proliferating cells, increased cell death and dramatic loss of germ cells. Although ibuprofen is clearly contra-indicated from 24 w of gestation onwards because of well-known risks of malformations, guidelines are prior to 24 w. Moreover, the consumption of ibuprofen during early pregnancy can occur due to unawareness of the pregnant state, or through ignoring the composition of the self-medicated drugs that are being used. The researchers also measured the ibuprofen levels in umbilical cord blood and showed that placental transfer of ibuprofen occurs as early as in the first trimester. Ibuprofen, like all NSAIDs, works by blocking cyclooxygenases (COX), key enzymes involved in the first rate-limiting step in the conversion of arachidonic acid into prostaglandins (PG). In the human fetal ovary, the constitutively expressed COX1 is primarily found in somatic cells, whereas the inducible COX2 is restricted to the periphery of the ovary where pluripotent germ cells are located, inferring COX2 involvement in ovarian. Despite evidence implicating PGs and COXs as critical factors in adult female reproductive function. Analgesics were found to induce cell death in human ovarian cancer cell lines. Researchers believed that exposure of the developing ovary to COX inhibitors may have toxic effects on germ and/or somatic cells.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a drug class that decrease fever, prevent blood clots and, in higher doses, decrease inflammation. Side effects depend on the specific drug, but largely include an increased risk of gastrointestinal ulcers and bleeds, heart attack and kidney disease. NSAIDs work by inhibiting the activity of cyclooxygenases enzymes (COX-1 and/or COX-2). The most prominent NSAIDs are aspirin, ibuprofen and naproxen, all available over the counter in most countries. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID), it works by reducing hormones that cause inflammation and pain in the body. Ibuprofen is used to reduce fever and treat pain or inflammation caused by many conditions such as headache, back pain, arthritis, menstrual cramps, or minor injury. Ibuprofen can increase your risk of fatal heart attack or stroke, it can also cause stomach or intestinal bleeding, which can be fatal. Around 28%-30% of pregnant women takes ibuprofen during pregnancy but many evidences and researches had indicated that use of ibuprofen during pregnancy may have adverse effect on the fertility of girl child. After studying this topic-ibuprofen, which is a non-selective inhibitor of COX, which decreases the cell proliferation and increases the rate of cell death in first trimester human fetal ovaries. This is done because fetal germ cells get affected. Ibuprofen, works by blocking cyclooxygenases (COX), key enzymes involved in the first rate-limiting step in the conversion of arachidonic acid into prostaglandin PG). Girls are born with a finite number of follicles in their ovaries and this defines their future reproductive capacity as adults.

RESEARCH SO FAR

To get answer of this emerging question-One research was done by Mitchell and colleagues from France and Denmark, on the impact of ibuprofen on developing ovaries using ovarian tissue taken from 185 terminated human foetuses aged between 7 and 12 w. In the first step of their research, the team had taken blood from the umbilical cords of 13 of the foetuses whose mothers had taken ibuprofen in the hours before termination, to reveal that ibuprofen did indeed cross the placental barrier. For each of the 185 foetuses, tissue was then cultured under multiple conditions, with one sample exposed to no ibuprofen and another one is exposed to different concentration of ibuprofen. After seven days,

compared to samples not exposed to ibuprofen, to the sample exposed to different concentration of ibuprofen they had an average of 50% fewer ovarian cells, and between 50 and 75% fewer "germ cells"–cells that develop into eggs. This was down to an increase in cell death and fewer cells multiplying. Further experiments showed that the damage began as early as two days after exposure to the ibuprofen for foetuses aged 8–12 w. After a five day recovery period for the samples, only a partial recovery from the effects of the ibuprofen was observed, but only germ cells appeared to bounce back. But Mitchell cautions that the situation in the body might differ from that in a dish, what level of germ cell loss would be tolerated before fertility is affected, or whether the ovaries could more fully recover over a longer periods.

RESULTS FROM RESEARCH

From this above research, they had drawn some results and they are:-

1. Ibuprofen crosses the placental barrier

When the fetus was exposed to ibuprofen at different range of concentration, ibuprofen concentration in the umbilical cord of 13 fetuses between 8 and 12 DW were measured. Ibuprofen concentrations were on average 0.37–14.5 μM. when pregnant women had ingested 800 mg of ibuprofen 2–5 h prior to termination of pregnancy. Following ingestion of a single dose of 400 mg, ibuprofen concentration was on average 0.83–6.95 μM in the umbilical serum. Ibuprofen was non-detectable when the women had not used the analgesic (n= 5 samples).

2. Ibuprofen impairs ovarian cell growth

Fetal ovarian explants (7-12 W) were exposed for a week to a range of ibuprofen concentrations from 1 to 100μM and the overall cell number was assessed. In uncultivated ovaries, the total number of cells per ovary increased exponentially from 2.6 × 105 at 7 DW to 1.3 × 106 at 12 DW. This number further increased during the 7 d of culture in control conditions. Where as when the organs were exposed to ibuprofen at the concentration of 10 μM for 7 d, the total ovarian cell count was significantly reduced (of −50% on average) compared to the unexposed controls, regardless of the developmental age of the explant. Although not significant for every age group, a reduction of the cell number was also observed with a 1 μM (−20% on average) and a 100 μM dose (−20% on average).

3. Ibuprofen suppresses ovarian prostaglandin E2 production

One day of exposure to ibuprofen at 10 μM significantly decreased by 66.3% prostaglandin E2 (PGE2) production by explants aged 7–12 DW. The average level of PGE2 in control samples was 353±73.9 pg/ml, while levels were reduced to 119±10.6 pg/ml in ibuprofen samples(P = 0.0062). No age-window of sensitivity for effect on PGE2 production was observed.

CONCLUSION

After studying many theories and researches, we can conclude that For a pregnant women, painkillers should be used only when it become necessary, and at the lowest dose for the shortest time possible. Currently we should advise that pregnant women should choose paracetamol or any other analgesics over ibuprofen because it is believed that paracetamol blocks the perception of pain in the mind of a person. It is generally safe at recommended doses but serious skin rashes can occur, that is also in very rare condition. It appears to be safe during pregnancy and when breastfeeding. Do not take ibuprofen after 30 w because ibuprofen crosses placental barrier in first trimester.

REFRENCES

1. Adams SS,Bough RG, Cliffe EE, Lessel B, Mills RF Absorption, distribution and toxicity of ibuprofen. *ToxicolApplPharmacol*1969
2. Bayne RA, Eddie SL, Collins CS, Childs AJ, Jabbour HN, Anderson RA. ProstaglandinE2 as a regulator of germ cells during ovarian development. *J ClinEndocrinolMetab*2009
3. Ben Maamar M, Lesne L, Hennig K, Desdoits-Lethimonier C, Kilcoyne KR, Coiffec I, Rolland AD, Chevrier C,Kristensen DM,Lavoue Vetal. Ibuprofen results in alterations of human fetal testis development. *Sci Rep*2017
4. Servey J, Chang J. Over-the-counter medications in pregnancy. *AmFamPhysician*2014
5. Black RA, Hill DA, Over The Counter Medications in pregnancy. Am Fam Physician, 2003
6. Rainsford KD: Ibuprofen-pharmacology, efficacy, safety. Inflammopharmacology,2009.

Panacea Journal of Pharmacy and Pharmaceutical Sciences 2018:7(2);055-101
International Journal ISSN: 2349 7025

MOLECULAR DOCKING APPROACH OF CATECHOL DERIVATIVES AGAINST ANTI-PARKINSONIAN DISEASE

Shikha Sharma*, Kapish Kapoor

School Of Pharmacy, Devi Ahilya Vishwavidhyalaya, Takshashila Campus, Khandwa Road, Indore-452001, M.P., India

E-mail: sharmashikha1293@gmail.com

ABSTRACT

Multicentric neurodegenerative disease which is characterized by loss of dopaminergic neurons as well as degeneration of non-dopaminergic systems such as nor-adrenergic, serotonergic and cholinergic systems is known as parkinson's disease. In the proposed study molecular docking study was done by using PDB code: 3PO7 and 200 catechol derivatives were studied as an anti-parkinsonian agent. Molecular docking study was performed on molegro virtual docker (version 6.0) and the result of molecular docking study revealed that most active compound was found to be CAT-18 to the active side of protein with amino acid Arg-42 and the mol dock score was found to be-176.924 and rerank score was found to be-116.055. this study revealed that above compound can be used further for *in vitro* and *in vivo* studies.

INTRODUCTION

Multicentric neurodegenerative disease which is characterized by loss of dopaminergic neurons as well as degeneration of non-dopaminergic systems such as nor-adrenergic, serotonergic and cholinergic systems is known as Parkinson's disease. Parkinson disease leads to progressive retrogression of motor fuction due to decline of dopamine producing neurons in sub-stantia nigra pars compacta. Genetic and environmental both are the major factors of PD. Primary symptoms of Parkinson's disease include: tremor, stiffness, impaired balance, muscle rigidity and gait. Followed by secondary symptoms that is: anxiety, depression and dementia.

EXPERIMENTAL

In this molecular docking study of Catechol derivatives, 200 catechol derivatives were taken and their energy minimization was done by using chem3d ultra 8.0. And pdb: 3PO7 was used for the binding of the molecules, after that molecular docking is done by using the software molegro virtual docker (version 6.0).

RESULT

Out of 200 catechol derivatives, compound CAT-18 showed best interaction with active site of protein with amino acid Arg-42 with the mol dock score-176.924 which revealed that CAT-18 has potential antiparkinsonian activity and it can be used for further *in vitro* and *in vivo* study.

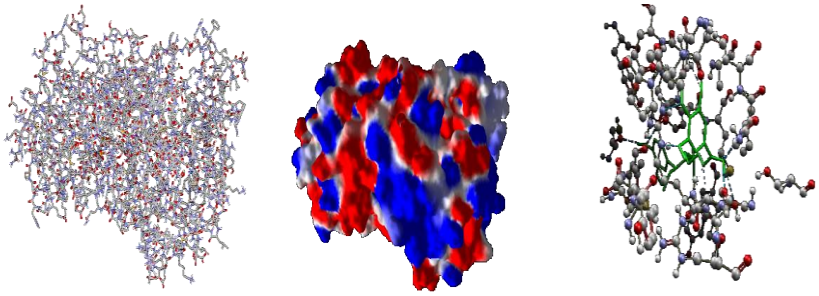

Figure 1. Showing Interactions of the most active compound with the protein and ligand

Table 1. Score comparison between top three compounds

Compound name	Mol dock Score	Rerank Score	H-bond Score
CAT-18	-176.924	-116.055	-12.5855
CAT-85	-151.365	-127.733	-5.9996
CAT-66	-138.187	-118.848	-17.4707

Table 2. Interaction comparison of the most active compound with the ligand

Ligand/Compound name	H-bond interactions
FAD_600 A	Arg-42,Glu-34,Tyr-66,ser-59,Ala-35,Met-436,Gly434,Val-235,Thr-426
CAT-18	Arg-42

CONCLUSION

The given study is valuable, inexpensive and important for further *in vitro* and *in vivo* studies. Selected Catechol analogues can be studied for their therapeutic potential in treating Parkinsonian diseases.

ACKNOWLEDGMENTS

I would like to thank Prof. Rajesh Sharma Head, School of Pharmacy, DAVV, Indore for providing the facility for the work.

REFERENCE

1. Journal of Ethno pharmacology Anti-Parkinsonian drug discovery from herbal medicines: What have we got from neurotoxic models Ju-Xian Song, Stephen Cho-Wing Sze, School of Chinese Medicine, LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China, December 2011.
2. Journal of medicinal chemistry; Interactions of Monoamine Oxidases with the Antiepileptic Drug Zonisamide: Specificity of Inhibition and Structure of the Human Monoamine Oxidase B Complex Claudia; Binda Department Genetics and Microbiology, University of Pavia, via Ferrata 1, Pavia 27100, Italy

ROLE OF HERBAL DRUGS ON NEUROTRANSMITTER FOR TREATING VARIOUS CNS DISORDERS: A REVIEW

Sourabh Nare *, Ankur Joshi, Sapna Malviya, Anil Kharia

Modern institute of Pharmaceutical Sciences, Indore-453111, M.P., India

E-mail: sourabhnare114@gmail.com

ABSTRACT

In the human body Neurotransmitters are chemical messengers and are associated with several CNS disorders. As agonist/antagonist/modulator to neurotransmitters to treat CNS disorders like Alzheimer's disease, Parkinson's disease etc. plant drugs can be used. The current review comprises the role of various neurotransmitters in CNS diseases and plants to treat them. To treat various CNS disorders this review compiles most of the scientific research related to the role of neurotransmitters and potential plants. Authors hope that researchers will utilize this current knowledge to explore and establish the potential herbal drugs to treat CNS disorders. By using references from major databases such as Medicinal and Aromatic Plants Abstracts, Chemical Abstracts, Google Scholar, Sci Finder, PubMed, Science Direct, Scopus, Springer Link, and books, review has been compiled without limiting the dates of publication. In the Pathophysiology neurotransmitters play an important role of various CNS disorders. For the potential drugs can be used to treat various CNS disorders. In this review we have discuss about the current knowledge of neurotransmitters, their role in Central nervous system disorders and herbal drugs can be used to treat these diseases.

KEYWORDS: Plant Drug, Phytotherapy, Phytoconstituents, Bioactive, Acetylcholine, GABA, Glutamate, Serotonin, Catecholamine.

INTRODUCTION

Gout is a common inflammatory disease which is characterized by acute arthritis and hyperuricemia due to disorder of purine metabolism. It is caused by the deposition of monosodium urate crystal in tissues, soft tissue masses, and other factors such as kidney stones and urate nephropathy are also responsible to cause arthritis. Attacks of pain,

erythema, and swelling of one or a few joints in the lower extremities are prominent clinical manifestations of acute gout. This disease is mainly occurring in men aged more than 50, affecting approximately 1–2% of adult men in the western world. The acute onset pain is in joint, erythema and swelling of the first metatarsophalangeal joint. Incidence of gout in India is not fully understood. A study from Vellore revealed that 15.8% of the affected patients are less than 30 y of age; urban Indian population is involved more than the rural population and due to increased prevalence of metabolic disorder in younger population, the first attack of gout occurs a ten times earlier to them. Additional Indian study showed that level of high uric acid is associated with laboratory and anthropometric parameters of metabolic syndrome. Uric acid levels increase in case of excessive intake of purine rich foods, fructose, or alcohol. Other causes of hyperuricemia are conditions associated with high cell turnover, that is, lymphoproliferative disease. In hyperuricemia, uric acid level is considered as>6.5 or 7.0 mg/dl (>416 mmol/l) in men and>6.0 mg/dl (>360 mmol/l) in women. The various treatments are available for gout but no one can cure; now the society is looking for other alternatives.

ETIOLOGY OF GOUT

Several factors are responsible for monosodium urate crystals to form. Gout is a complex disease. There are a variety of factors that can play a role in causing the gout Certain conditions, such as blood and metabolism disorders are also a cause to produce too much uric acid. Drinking too much of alcohol may also leads to excess uric acid. Certain foods can also cause gout when you eat too much of them These include: shellfish, red meat, organ meat, sweet juices and salt. There are different types of diseases which may lead to cause gout such as type-2 diabetes, hypertension, hyperlipidemia, cardiovascular disease, renal disease, and obesity suggest that gout and its necessary precursor hyperuricemia may play an important role in the demonstration of the metabolic syndrome and some other factors such as trauma, repetitive microtrauma, arthritis, infection, lack of tissue perfusion, lower blood pH, or lower tissue temperature act as the local factors.

TREATMENTS OF GOUT

Gout flare medications are include colchicine, non-steroidal anti-inflammatory drugs and steroids, which can be taken together in severe cases and they are most efficient when taken early after the flare onset.

Allopathic treatment classified on the basis of duration

Short-term therapy

Colchicine: If taken before 12 h after flare onset, 1.8 mg of colchicine has been shown to be more effective than the traditional higher doses. In some conditions, the combination of colchicine with other drugs such as cyclosporine, ketoconazole, erythromycin, diltiazem or verapamil reduce the dose of colchicine.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Aspirin, celecoxib, diclofenac, diflunisal, etodolac, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac and tolmet are the drugs which belong to the class of NSAIDs. Nonsteroidal anti-inflammatory drugs block the COX enzymes and reduce prostaglandins throughout the body and their efficacy is largely accepted.

Steroids: Oral, parenteral, and intra-articular steroids are used to treat acute gout and corticosteroids such as prednisone are generally given because this is a safer approach than using NSAIDs. Adrenocortcotropic hormone can also be injected in the muscle or intravenously for the treatment of gout.

IL-1 Blockers: are the drugs which reduce the level of urate in serum and then treat gout, IL-1 inhibition for acute gout are those for whom conventional flare therapies are ineffective. Various drugs are used such cryopyrin, rilonacept, canakinumab, anakinra, triamcinolone acetonide and canakinumab. Among these drugs, canakinumab is more effective than a single dose of intramuscular triamcinolone for treating an acute gout flare.

Single Therapy: In a prospective study of joint aspirations in patients with gout on urate-lowering therapy, the recommended therapeutic Serum Urate Lowering drugs are.

Long-term treatments

Allopurinol: Allopurinol is an oral xanthine oxidase inhibitor, first introduced to the clinic in the sixties. Perhaps one of the more contentious interactions between rheumatologists and nephrologists relates to allopurinol dosing in the

setting of CKD. Allopurinol and other xanthine oxidase inhibitors should not be prescribed with azathioprine and 6-mercaptopurine, as xanthine oxidase is involved in the metabolism of these drugs.

Febuxostat: Febuxostat was the first new urate-lowering drug to be approved in the United States in over 40 y. It is a xanthine oxidase inhibitor and therefore has the same mechanism of action as allopurinol. It may be an option if patient develops side effects from allopurinol or has kidney disease. Like allopurinol, febuxostat decreases the amount of uric acid made in the body. It is also started at a lower dose, which may be increased if uric acid levels remain high. Side effects can include nausea and joint or muscle pain.

Probenecid: Probenecid has been the first commercialized urate lowering drug and was at first a very popular drug. When allopurinol became available, probenecid was much less used because it had to be given in divided doses and required high fluid intakes and adjustment of the urine pH. It acts on the kidneys to help the body to eliminate uric acid. The medication is taken daily and may be combined with antibiotics to boost effectiveness. The common side effects include nausea, kidney stones, skin rashes, upset stomach and headaches.

Lesinurad: Lesinurad acts orally and helps the body to eliminate uric acid. It is used with xanthine oxidase inhibitor (XOI), such as allopurinol and febuxostat to increases the effects for those people whose gout is not controlled by optimally-dosed XOIs alone. The common side effects of this drug include headache, flu symptoms, increased level of blood creatinine, gastroesophageal reflux disease, kidney-related side effects and kidney stones.

Pegloticase: This is used when standard medications are unable to lower the uric acid level, a condition known as refractory chronic gout. It is an effective than other drugs and it reduces uric acid quickly and lowers its levels than other medications. The drug is administered every two weeks by intravenous (IV) infusion. Side effects of this drug can include gout flares, nausea, painful knee, sore throat, constipation, infusion reactions, vomiting and chest pain.

Combined therapy

In severe stage of gout, short-term therapy is not useful for treating the gout. Thereafter in this stage, we use the combination therapy of short-term and long-term medicines for the treatment of chronic or severe gout.

Treatment of gout with herbal plants

Herbal plants are the best alternative source for the treatment of gout, the list of used plants is given below in Table

Table 1: Herbal Plants for the Treatment of Gout.

S. No.	Plant used	Botanical name	Family	Chemical constituents
1	Cherry tree	*Prunus avium*	*Rosaceae*	Synogenic glycosides
2	Garlic	*Allium sativum*	*Liliace*	Allyl propyl disulfide
3	Lemon tree	*Citrus limonis*	*Rutaceae*	limonin, Citral
4	Onion	*Allium sepa*	*Amaryldaceae*	Quercetin, citral
5	Potato	*Solenum tubersoma*	*Solanaceae*	Starch, solasodine
6	Oats	*Avena sativa*	*Poaceae*	Avenine,trigonelline
7	Dandelion	*Taraxacum officinale*	*Compositae*	Inuline
8	Linden	*Tilia cordata*	*Tiliaceae*	Fanesol
9	Willow	*Salix fragilis*	*Saliaceae*	Salicine
10	Red wine	*Vitis venifera*	*Vitaceae*	Viniferins resveratrol
11	Birch	*Betula alba*	*Poaceae*	Hyproside myricetin

Marketed formulations of herbal drugs for the treatment of gout

The list of marketed drugs has given below in table 2

Table 2. List of marketed formulations of herbal drugs for the treatment of gout

S. No	Common name	Marketed Formulation
1.	Ashwagandha	Ashwagandha Powder
2.	Ashwagandha	Ashwagangharishta
3.	Liquarice	Respinova
4.	Liquarice	Yasti madhu
5.	Oroxylum Indicum	Anxiocure
6.	Shillaki	Joint AID plus

CONCLUSION

Guidelines for the management of gout developed by the ACP primary care in comparison to the rheumatology society gout guidelines groups are discordant, despite assessment of largely the same evidence, with the exception of trials of pegloticase. To understand gout, and consequently to manage it, has been a challenge to the skill of physicians along the history of medicine. Recent advances in this field that took the shape of continuous progress, have recently witnessed quantum leaps. There are many therapies which are used for the treatment of gout. The aim of this review is to introduce the current therapy for gout. Various therapies have been recommended to treat the gout, such as allopathic treatment, treatment with herbal marketed formulation, physiotherapy, acupuncture and laser therapy. Now there is a resurgence of interest in improving its management. This review article may be beneficial for future aspects to treat the gout disease.

REFERENCES

1. Wang W, Xu D, Wang B, *et al.* Increased Risk of Cancer in relation to Gout: A Review of three Prospective Cohort Studies with 50,358 Subjects*. Mediators Inflamm.* 2014; 2015: 6p.
2. Pande I. An Update on Gout. *INJR.* 2006; 1(2): 60–65p.
3. Danda D, Mathew A, Mathew J, *et al.* Clinical Profile of Young Onset Gout. *J Indian Rheumatol Assoc.* 2005; 13: 51–53p.

FORMULATION AND EVALUATION OF CHRONOMODULATED DOSAGE FORM OF SALBUTAMOL SULFATE

Priyanshi Chourasiya, Himani Nagwadia, Pravin K. Sharma, G. N. Darwhekar

Acropolis Institute of Pharmaceutical Education and Research, Indore-452001, M.P., India

E-mail: priyanshichourasiya@gmail.com

ABSTRACT

Chronotherapy deals with the release of drug in the body during its greatest need and is allowed to match with the circadian rhythm of disease. There are certain conditions, in which drug has to released after a particular lag time. Salbutamol sulfate used to treat asthma undergoes first pass metabolism and approximately 50% of drug on oral administration is absorbed from intestinal tract with slower onset of action and after 2 h of intake it reaches to a peak therefore to achieve the effect of drug after a desired lag time the study was aimed to develop and evaluate chronomodulated dosage form of salbutamol sulfate using ethyl cellulose as a polymer and other excipients. The drug was incorporated in the core, to be released promptly at the time of asthmatic risk. The tablet was prepared by wet granulation method and was evaluated using various pharmaceutical parameters like hardness(4 kg/cm^2),

Thickness(0.2 mm), UV spectra showed an absorbance of 1.597 at wavelength of 268 nm and the *in vitro* drug release from coated tablet was found to be 89.13% after a particular lag time of 5 h which complies with chronotherapeutic effect.

KEYWORDS: Chronomodulated, Salbutamol sulfate, Circadian rhythm, Nocturnal asthma.

INTRODUCTION

Circadian rhythm

Circadian rhythm displays the endogeneous oscillation of 24 h. The body functions according to the biological process knows as circadian rhythm. The body functions such as sleep awake cycle, hormone production, body temperature, metabolism, blood pressure, etc is controlled by circadian rhythm.

Chronomodulated drug delivery system

Chronomodulated drug release is a system where the drug is released suddenly after a well-defined lag time or time gap according to the circadian rhythm of disease states. No drug should be released from this device within this lag time. There are some conditions in which the right amount of drug has to be administered at right site and at the right time. As in conventional dosage form the drug release commences as soon as the drug is administered but certain conditions demand the release of drug after a lag time, in such case if the chronomodulated dosage form is administered at a specific time and gets released after a particular lag time would result into a promising chronotherapeutic outcome.

Advantages of chronomodulated dosage form

- Extended day and night time activity.
- Reduce side effects.
- Reduced dosage frequency.
- Improved patient compliance.
- Drugs adapts to suit cardiac rhythms to body function or disease.

Disadvantages of chronomodulated dosage form

- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need for advanced technology.

Asthma

Asthma is a chronic inflammatory disorder of the airways characterized by airflow obstruction within the lungs, Airway inflammation, chest tightness, breathlessness, coughing, wheezing, etc. The condition of asthma worsens during early morning in the interval of 4:00 am to 5:00 am. Chronomodulated dosage form of salbutamol sulfate can be promising method for the treatment of such type of condition.

MATERIALS AND METHOD

Salbutamol sulfate was obtained as a gift sample from Modern Laboratories, Indore. Microcrystalline cellulose, Starch, Magnesium stearate, Talc, Sodium starch glycolate, ethyl cellulose, Propylene Glycol, Acetone from AIPER, Indore.

Preformulation Studies

Organoleptic properties

The colour and odour of the drug were characterized and recorded using descriptive Terminology.

Solubility

Solubility of Salbutamol sulfate in different solvents was studied.

UV spectroscopy

Salbutamol sulfate is soluble in Methanol. Sample solution of drug (2 to 10µgm/ml) was pepared in methanolic water(2:8). Then scan was run in the range of 200 to 400 nm on uv spectrophotometer (shimadzu 1800) and spectrum was compared with the standard spectra of drug. The wavelength of drug reported in Indian pharmacopeia is 276 nm.

Formulation of chronomodulated dosage form of salbutamol sulfate

The tablets were prepared by wet granulation**.** The salbutamol sulfate,sodium starch glycolate, microcrystalline cellulose and starch solution were mixed together. Granules were prepared by wet granulation method and then dried at 60˚C for 2 h the dried granules were passed through sieve no.24. The resultant granules were finally lubricated with magnesium stearate and talc was added to improve the flow property. Granules were compressed into tablets using tablet punching machine. The core tablets were then coated with solution of ethyl cellulose in acetone.

Table 1. Formulation ingredients

S. NO	Ingredients	Quantity
	Salbutamol sulfate	120 mg
2	Microcrystalline cellulose	2.4 gm
3	Starch	2.4 gm
4	Magnesium stearate	30 mg
5	Sodium starch glycolate	60 mg
6	Talc	30 mg
7	Ethyl cellulose	5 gm
8	Propylene glycol	0.1 ml
9	Acetone	50 ml

Evaluation of the tablets

Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The Hardness of salbutamol sulfate tablets was tested by **Monsanto hardness tester.** The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness was recorded.

Thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using vernier calipers. It was determined by checking the thickness of 3 tablets.

Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of the drug. The weight variation is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The percentage difference in the weight should be within the permissible limits (±7.5%). The percent deviation was calculated using the following formula, Percentage deviation = (individual weight-average weight/average weight)×100

In vitro dissolution study

In vitro drug release from coated tablets was carried out using IP paddle apparatus at 50rpm and 37±0.5°C. HCl (0.1 N) and phosphate buffer (pH 6.8) were used as dissolution medium. Initially tablets were subjected to dissolution in 0.1 N HCl for 2 h and after that media was changed to phosphate buffer (pH 6.8). The samples were withdrawn at regular intervals and analyzed by UV spectrophotometer (Shimadzu 1800) at 276 nm for the presence of the drug.

RESULT

Preformulation studies

Organoleptic properties of salbutamol sulfate

Drug was observed to be a white or almost white, crystalline powder.

Solubility

The drug was freely soluble in water, slightly soluble in ethanol and in ether, very slightly soluble in dichloromethane.

UV Spectroscopy of Salbutamol sulfate

The UV spectra of salbutamol sulfate in methanolic water showed an absorption of 1.597 at wavelength of 268 nm.

Weight variation for tablet

The weight variation is done by weighing 20 tablets individually,calculating the average weight and comparing the individual weights to the average. The percentage difference in the weight was within the permissible limits (±7.5%).

Collective weight	Average Weight
1.42 gm	0.071 gm

Hardness of tablet

The hardness was found to be 4 kg/cm^2.

Thickness of tablet

The average thickness of tablets was found to be 0.2 mm.

In vitro dissolution study of tablets

In vitro drug relese from coated tablets was carried out using IP paddle apparatus at 50rpm and 37±0.5°C. HCl (0.1 N) and phosphate buffer (pH 6.8) and the samples were analyzed by UV spectrophotometer at 276 nm and results were found to be as presented in table 2.

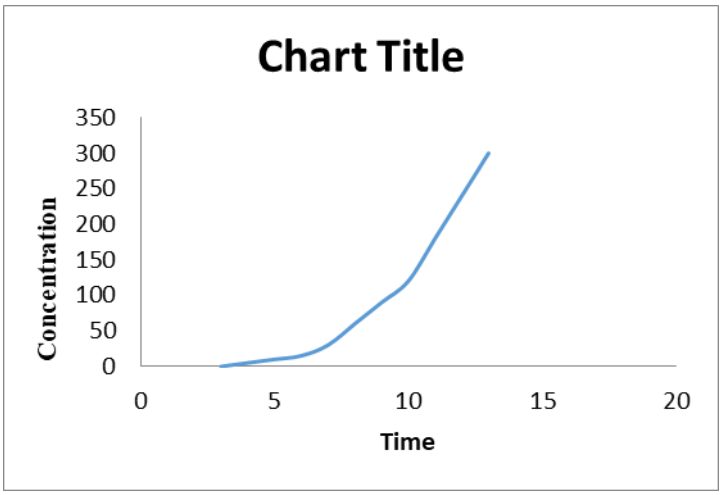

Figure 1. Chronomodulated release of salbutamol sulfate

Table 2. Observation table for dissolution study

S. No	Time	Absorbance		Average absorbance	Conc.	Amount of drug release	% drug release	Cumulative % release
		1	2					
1	5	0.364	0.348	0.356	6.262	5.635	6.261	6.261
2	10	0.350	0.371	0.360	6.337	5.703	6.336	12.597
3	15	1.696	1.712	1.704	31.226	28.103	31.225	43.792
4	30	0.027	0.035	0.031	0.244	0.219	0.243	44.035
5	60	0.235	0.243	0.239	4.096	3.686	4.095	44.13
6	90	0.482	0.462	0.472	8.411	7.57	8.41	52.54
7	120	0.492	0.483	0.487	8.698	7.828	8.698	61.238
8	180	0.502	0.507	0.504	9.031	8.128	9.031	70.269
9	240	0.512	0.523	0.517	9.253	8.328	9.25	79.522
10	300	0.536	0.539	0.537	9.614	8.653	9.61	89.13

CONCLUSION

It concluded that, Chronomodulated drug release over a period of 5-6 h was achieved. Therefore the study proved that coated salbutamol sulfate can be successfully used as a time dependent modified chronopharmaceutical form.

REFERENCES

1. Asiniparthi Madhuri, *et al.*, "Formulation and Evaluation of Chronomodulated Drug Delivery of Montelukast Sodium", Global Journal Pharmaceutical Science, vol 1, 2017, 001-008.
2. Rasve Ganesh, *et al.*, " Pulsatile Drug Delivery System: Current Scenario", International Journal of Pharma and Bio Sciences, vol 2, 2011, 332-343.
3. Gandhi Mayur, *et al.*, "Review Article on Pulsatile Drug Delivery System", International Journal Pharmaceutical Sciences Review and Research, vol 2, 2014, 251-255.
4. B Haritha, "A Review on Evaluation of Tablets", Journal of Formulation Science and Bioavailability, vol 1, 2017, 1-5.
5. agadeesan M, "A study on concurrent drug utilization evaluation of antiasthmatic drugs in the tertiary care hospital", International journal of novel trends in pharmaceutical sciences, vol 6, 2016, 14-19.
6. Prasanth V. V, *et al.*, "Formulation and evaluation of Salbutamol sulphate microspheres by solvent evaporation method", Journal of Applied Pharmaceutical Science, vol 1, 2011, 133-137.
7. Anusha V, *et al.*, "Formulation and Evaluation of Chronomodulated Pulsatile Drug Delivery System of Salbutamol Sulphate", International Journal for Pharmaceutical Research Scholars, vol 4, 2015, 157-165.
8. Muzaffar Sadaf, *et al.*, "Formulation and evaluation of pulsatile drug delivery system", International journal of pharmacy and analytical research, vol 1, 2015, 51-59.

9. Gandhi Mayur, *et al.*, "Review Article on Pulsatile Drug Delivery System", International Journal of Pharmaceutical Sciences Review and Research, vol 26, 2014, 251-255.
10. Keerthi S., *et al.*, "Formulation and Evaluation of Pulsatile Drug Delivery System of Anti-Asthmatic Drug", American Journal of Pharmtech Research, vol 4, 2014, 798-809.
11. Rohitash Kumar, *et al.*, "Formulation and Evaluation of Two-Pulse Drug Delivery System of Amoxicillin Trihydrate", Tropical Journal of Pharmaceutical Research, vol 13, 2014, 1593-1600.
12. Satani R. R., *et al.*, "Review on recent trends in press-coated pulse drug delivery system", International Bulletin of Drug Research., vol 4, 2014, 60-91.
13. Patel Tejaskumar, *et al.*, " Formulation and Evaluation of Erodible Pulsatile Drug Delivery System of Salbutamol Sulphate for Nocturnal Asthma" International journal of research article pharmaceutical innovations, vol 3, 2013, 25-30.
14. Sonje Abhijit, *et al.*, "Evaluation of Pulsatile Tablet in Capsule Pulsatile Release Device", International Journal of Pharmaceutical Sciences Review and Research, vol 20, 2013, 215-218.
15. Amol M, "Design andamp; evaluation of pulsatile drug delivery system of atenolol for chronomodulated therapy", International Journal of Pharma and Bio Sciences, vol 3, 2012, 1–8.

DISEASE PERSPECTIVE AND PROSPECTIVES IN CHRONOTHERAPY

Ritu Chaurasia,* Anupam Mishra, G. N. Darwhekar

Acropolis Institute of Pharmaceutical Education and Research, Indore-452001, M.P., India

E-mail: rituchaurasia123456@gmail.com

ABSTRACT

Body functions in human such as behavior, sleep pattern, hormone production, metabolism, physiology, etc. are regulated by circadian rhythm. Some of the diseases like myocardial infarction, bronchial asthma, peptic ulcer, rheumatoid arthritis, hypertension, cancer show circadian pattern and in such conditions drug has to be administered according to circadian rhythm of disease. For management of such conditions chronotherapy plays an important role. Chronotherapy deals with the treatment method in which the drug is released according to rhythm of disease and to get required therapeutic output with reduced side effect. Recent advancements have been made using different dosage forms, which has proved to be an effective way to treat the disease. This article focus on the detail about the circadian rhythm, Chronotherapy, the biological cycle associated with the disease and the treatment for the management of the disease that require the drug to be released at specific time and site by choosing the optimum time to achieve the desired effect and undesirable effect to be minimized.

KEYWORDS: Chronotherapy, circadian rhythm, Myocardial infarction.

INTRODUCTION

In a day, human body functions vary considerably. These variations leads to change in disease state as well as in plasma drug concentration. Circadian rhythm influences the disease state. There are some hormone which are released more during night hours while, some get released in the morning. There are some diseases which worsens during a particular time in a day such as the chances of asthmatic attack is more around 4'o clock early in the morning. As this diseases are depend on circadian rhythm and biological clock of the body.

Circadian rhythm

It is a 24 hour cycle which includes physiological, behavioral, sleep awake cycle, hormone production, metabolism, body temperature, heart rate, blood pressure, blood flow, plasma concentration of hormone, stroke volume, peripheral resistance, moreover many functions of liver and kidney like metabolism, first pass effect, pH, urine volume etc. of the human body.

Chronotherapy

Chronotherapy deals with such disease which require the proper amount of drug release at specific time and at specific site. The optimization of drug effects and minimization of toxicity by timing medications with regard to biological rhythms is called chronotherapy. Chronotherapeutics is predict as time dependent variation in the pharmacokinetics of drugs as well as the susceptibility of target tissues due to temporal organization of physiochemical processes and functions of the body as circadian and other rhythms.

Advantages

1. Chronotherapy effect increase the patient sleep for several hours.
2. The point of work at which the chronotherapy work can be predicted.
3. The proper amount of dose can be administered at the time of its requirement.
4. It maintains the sleep awake cycle.
5. Drugs adapts to suit circadian rhythm to body function or disease

Disadvantages

1. The patient with hot and cold may feel hot and cold for sometimes.
2. Regular consultancy from the doctor should be taken to avoid side effect.
3. Proper dose of drug should be administered in proper interval of time.

Some of the diseases that follow chronotherapy are

Myocardial infarction

The event of Myocardial infarction is expected more during the start of daily activity or last in afternoon and early evening. Such temporal pattern results from circadian rhythm. This type of conditions require preventive and therapeutic measures to be made accordingly to optimize the outcomes. Calcium channel blocker chronotherapies have been developed for the treatment of myocardial infarction.

Bronchial Asthma

The symptoms of Bronchial asthma are highest from midnight to early morning which shows its peak at around 4'o clock am. Therefore it is important to administer the right amount of drug at the right time to match the circadian rhythm of the disease.

Peptic Ulcer

Functions of the gastrointestinal tract follow circadian rhythm like gastric emptying and small bowel motility is slower at night and gastric acid secretion is highest at night. Suppression of secretion of acid is important to overcome this problem. Bedtime H2 receptor blockade using chronotherapy heals the ulcer.

Rheumatoid Arthritis

The characteristics feature of rheumatoid arthritis is morning stiffness and the symptoms worsen during morning and afternoon. Non-steroidal anti-inflammatory drugs taken late at night have proven to be best for relieving the morning pain and stiffness of rheumatoid arthritis.

Hypertension

Blood pressure gets accelerated during morning and declines during sleep at night. The high blood pressure cannot be controlled if the medication is taken early in the morning. Therefore antihypertensive drug is administered at bedtime so that it shows its effect in the morning.

Cancer

Studies suggest that if cancer drugs are administered carefully at selected time, chemotherapy could be more effective and less toxic. Drug toxicity, Severity pattern, Average dose intensity, Maximum tolerated dose, Tumor response quality, Frequency and the survival of patients with the cancer gets affected meaningfully by Circadian chemotherapy timing.

CONCLUSION

The importance of biological rhythm of drug is determined in chronotherapy. Application of chronotherapeutic drug delivery system are better treatment for the disease such as myocardial infarction, bronchial asthma, rheumatoid arthritis, hypertension and cancer. Timing of drug administration in disease therapy has significant impact on the success of the treatment and this therapy has become the new approach in the drug delivery system.

REFERENCES

1. Sumant Saini *et al.*, "Chronotherapy: A Review", International Journal of Drug Delivery Technology 2014;4(3);47-57
2. Sajan J.,"Chronotherapeutics and Chronotherapeutic Drug Delivery Systems", Tropical Journal of Pharmaceutical Research, October 2009; 8(5): 467-475
3. Rajendra Awasthi *et al.*, "Chronotherapy: Science and technology of drug scheduling on the basis of biological rhythm", Journal of Chronotherapy and Drug Delivery, Vol 1, Issue 1, 2010: 09-18
4. Latha *et al.*, "Chronobiology and Chronotherapy of Hypertension–A Review" International Journal of Health Research, September 2010; 3(3): 121-131
5. Singh Anamika, *et al.,* "Pulsatile Drug Delivery System: an Approach of Medication according to Circadian Rhythm", Journal of Applied Pharmaceutical Science, vol 2, 2012, 166-176.
6. Bhat Amit, *et al.*, "formulation and evaluation of chronopharmaceutical drug delivery of theophylline for nocturnal asthma", International Journal of Pharmacy and Pharmaceutical Sciences,Vol 3, 2011, 183-185.
7. Sadaphal K. P., *et al.,*"Formulation and evaluation of pulsatile drug delivery system for chronobiological disorder: Asthma", International Journal of Drug Delivery, vol 3, 2011, 348-356.
8. Tawar Mukund G., *et al., "Formulation* and Evaluation of Chronomodulated Drug Delivery System", Research Journal of Pharmaceutical Dosage Forms and Technology, vol 2, 2010, 100-102.
9. Shah Viral, *et al.*, "Formulation and Evaluation of pulsatile drug delivery of salbutamol sulfate", International journal of pharmaceutical sciences review and research, vol 4, 2010, 59-63.
10. Singh Rupali., "Review on Chronotherapeutics–A New Remedy in the Treatment of Various Diseases" European Journal of Biological Sciences 2(3): 67-76

A REVIEW ON-HERBAL TREATMENT USED IN POLYCYCTIC OVARION SYNDROME

Poojashree Verma *, Shivendra Raghuwanshi, Ankur Joshi, Narendra Vyas, Sapna Malviya, Anil Kharia

Modern Institute of Pharmaceutical Sciences, Indore

E-mail: pooja11.pharma@gmail.com

ABSTRACT

Polycystic ovarion syndrome is the one of most common metabolic and reproductive disorder of women it affecting 5 to 10% of women in the age group 12-45 y polycystic ovarion syndrome is related to an imbalance in these sex hormone such as androgen and estrogen the condition is overviewed and characterized by hyperandrogenism and ovulatory dysfunction and olio and amenorrhea, acne and thinning hair on scalp psychological stress, and pregnancy complication. Now there are lots of treatment available such as progestin birth control pill, metformine their function regulate the ovulation and increasing menstrual flow but lots of side effects including lactic acidosis, weight gain and loose and hepatic toxicity, mood changes and bloating. This review study focus on to herbal remedies used in pcos. herbal remedies easily available and limited side effect. Herbal medicines have been shown to improve hormone balance in PCOS and may positively affect menstrual regularity.

KEY WORDS: Polycystic Ovarion syndrome,Herbal Treatment, toxicity

INTRODUCTION

Polycystic ovarian syndrome is a common endocrine system disorder among women of reproductive age, most women with PCOS have many small cyst on their follicle hence it is called PCOS. The cyst are not harmful but lead to hormonal imbalance. One hormone triggers the function of other hormone. Now a day's PCOS appear rising in India 5% and 10% of women in their reproductive age. The incidence increasing may be due to unhealthy life style polycystic ovary syndrome is originally called as the Stein–Leventhal syndrome. Polycystic Ovarian Syndrome (PCOS) is a serious disorder in women in which the ovaries become enlarged with many 'cysts' which are in fact small undeveloped follicles. Over time there is thickening and fibrosis of the ovarian casing which prevents any follicles which do ripen from being released. PCOS is associated with anovulation and menstrual irregularities, infertility and insulin resistance. There may be acne, hirsutism and weight gain. As the condition progresses it may become associated with dysfunctional uterine bleeding, obesity, Type 2 diabetes, endometrial cancer, high cholesterol and cardiovascular disease

.

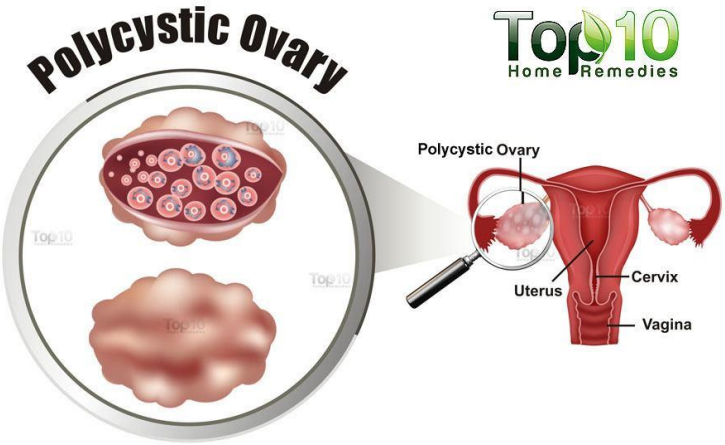

Figure 1. Difference between polycystic ovary and normal ovary

CAUSE

- Excess insulin
- low Grade inflammation
- heredity
- excess androgen

SYMPTOMS

- Infertility
- Gestational Diabetes
- Miscarriage
- Non alcoholic hepatitis
- Metabolic Syndrome
- Type 2 diabetes
- Sleep Apnea
- Depression, Anxiety, eating Disorder
- cancer in uterine lining(endometium cancer)-
- Menstrual Irregularties

ALLOPATHIC THERAPY FOR PCOS

1) Naferelin

2) Trigilitazone
3) Clomiphen
4) Metformine
5) Spirinolactone
6) Laproscopy

According to modern medicine there is no cure for pcos have their own side effects like nausea, vomiting, sleep disturbance unusual vaginal bleeding like nervousness, fatique breast tenderness, diarrhea, constipation, stomach bleeding, change in appetite, weight gain,acne, vision disturbance treatment available for pcos are birth control pill to regularize period, metformine to reduce and improve resistance and fertility treatment used for induce ovulation and surgical prtocedure and medication to reduce hirsutism and life mofication also the manage of PCOS EXAMPLE Regular excersise and meditation and diet, reduce the blood sugar level eat balanced diet and use low glycemic healthy diet

PATHOPHYSIOLOGY OF PCOS

PCOS is a condition that originates possibly at the time of puberty due to interplay of

1) Obesity and excess of ovarion androgen production, due to hyperinsulinemia
2) Intrauterine environment
3) Genetic factor both X linked autosomal dominant modes of inheritance
4) Disturbance to hypothalamic pituitary ovarion
5) Obesity is strongly associated with PCOS, it range from 30%-75%

Obesity induced,through the path of insulin resistance,high level of insulin realated growth factor these will stimulate theca cell to produce(SHBG) synthesis by liver cell,there by raising the proportion of free circulating testosteroneFactor which is responsible for genetic factor this may increased the chance of hypothalamic pituitary ovaries dysfunction in pcos and increased the level of gonadotropin releasing hormones and increased the level of LH and FSH level hormone also include the this may be leads to hyper androgen level.

Table 1. Herbal medicine used in polycystic ovarion syndrome

S. No	HERBAL DRUG NAME	ACTIONS
1	Chaste Berry	• It help to stimulate the function of pituitary gland • Pituitary gland is responsible for the release of luteinizing hormone • Hormonal Imbalance • 4)Aadaptogen
2.	Dandelion Root	• Clean up and stimulant the production of SHGB • Free testosterone level • Menstrual Irregulaaties • Liver Detoxifier • Clean up the liver and git rid of any build up of hormone
3.	Milk Thistle	• Reduce excess level of estrogen • Reduce insulin Resistance • Promote a Healthy liver by damaged liver cell and protecting the liver against damage
4.	Licorice	• Decrease the testosterone level • Increase the ovulation • Decrease the acne and hair • Stress Reducing
5.	Saw Palmetto	• Antiestrogenic

		• Decrease the testosterone
		• Block the process of testosterone turning into DHT
5	Stinging Nettle	• Increase the production of SHBG
		• (Sex Hormone binding globulin)
		• Reduce the level of testosterone
6	Flax Seed	• Increase the SHBG level
		• Metabolize estrogen
		• SHBG and High Estrogen
7	White Peony	• Influence of low progesterone level
		• Reduce the high endrogen level
		• Stabilize the Mensuration Cycle
8.	Gymnema	• Antidiabetic effects
		• Insuline modulating activity
		• It regulate the insulin level and control the sugar level
		• Reduce the carbohydrates craving
9.	Blue Kohesh	• Prevent the excessive menstrual bleeding
		• Activate the menstruation
		• Minimize the menstrual cramping
		• It regulate the menstrual cycle
		• Stimulate the uterine activity
10	Red Clover	• These herb has isoflaven which change to phytoestrogen
		• Blood purifier
		• Treat acne
11	Hops	• Relive stress level
12	Tribulus	• Ovarion Stimulant
		• Normalize the ovarion function and cycle
13	Black Kohesh Root	• Strong effect on endocrine system
		• Pms effects
		• Use in Excessive menstrual cramps
		• Hormone related symptoms
14	St john Wort	• Treat Depression
		• Hormonal Balance
15	Goat Rue	• Anti diabetic
16	Dong Quie	• Help to return normal hormone level
		• Strengthen the immune system
		• Normalise the menstrual cycles
17	Red Raspberry Leaf	• Strengthen the female reproduction system
		• Stop Heavy menstruation Bleeding
		• Strengthen the lining of uterus
18	Evening Primerose oil	• Balance hormone level such as progesterone and estrogen level
		• It helpful in women women have high level of estrogen
19	Coconut oil	• Anti oxidant
		• It regulate blood sugar level
		• Reduce insulin level
20	Castor oil	• Enhance circulation and lymph flow in the area applied to regulate hormonal and nutrient delivery
		• Body detoxifier

21	Royal Jelly	• Support the ovarion function • Help to regulate menstrual Irregularities • Herbal Supplement
23	Aloe Vera Juice	• Reduce the cholesterol level • Restoring the ovarian approaches • Effect on ovarian function • Help to relive the PCOS symptoms
24	Amla Juice	• Detoxifier and reduce the cholesterol level • Anti inflammatory effects
25	Palm Jaggery	• It regulate the insulin and blood sugar level • Passes low glycemic index and boost the energy level • High level of insulin common in pcos patient unrefined type of jaggery
26	Jeera water	• Decrese blood sugar level • Antioxidant
27	Kalonji seed	• Anti inflammatory • Anti Diabetic • Estrogenic Property
28	Fenugreek seed	• Decrease the effect of PCOS and promotes glucose metabolism • Help to regulate the hormone in the body and glucose metabolism • Regulate the hormone in the body
29	Sesame seed	• Nutrient benefit of pcos • Help to regulate blood glucose level
30	Fennal seed	• Anti Hirsutism • Decrease the androgen level
31	Pumpkin Seed	• Help to manage high cholesterol • Remove excess and treat hirsutism • Acne • Weight loose
32	Cinnamon	• Increase the insulin sensitivity • Boost the colries • Decrese the lipid and cholesterol level
33	Spearmint Tea	• Reduce the testosterone level • Increase the FSH and LH level
34	Bitter Gourd	• Lower the sugar level
35	Honey	• Reduce Hunger
36	Holey Basil	• Stress Reliver • Antioxidant • Anti inflammatory • Lower the blood glucose

Alternative Treatment

1) Acupuncture
2) Life style modification
3) Yoga
4) Limit sugar intake
5) Exercise
6) Dietary intake

7) Increase water intake
8) Weight control and weight loss
9) Don't Smoke
10) Caring for skin and hair

FUTURE COMPLICATION

1) Cardiovascular disorder
2) Diabetes mellitus
3) Metabolic syndrome
4) Endometrium cancer

YOGA STEP CURE FOR PCOD

1) Dhanurasana
2) Sarwagasana
3) Anulom vilome
4) Kapal Bhati
5) Bhujangasana

CONCLUSION

Polycystic ovary syndrome is a one of the most common disorder of female endocrine disorder which may leads to infertility and acne and obesity complex disorder. long term used Allopathic medicine may cause the serious side effects. Long-term consequences of PCOS, which include type-2 diabetes and cardiovascular disease, can be treated with antidiabetic drugs and statins Polycystic Ovarian Syndrome (PCOS) is one of. Herbal drugs have promising role in treatment of PCOS and shows steady effect with minimal side effects. Herbal drugs enhance immunity of the body and also regularize menstrual cycle without fluctuating hormonal level. For regulating menstrual cycle, various poly herbal supplements are being used in India. Herbal treatment and excersise and yoga practice is great cure for pcod.

REFRENCES

1. Umland EM, Weinstein LC, Buchanan EM. Menstruation-related disorders. In: DiPiro JT, Talbert RL, Yee GC, *et al.*, editors. Pharmacotherapy: A Pathophysiologic Approach.8th ed. New York: McGraw-Hill; 2011. p. 1393.
2. Lin LH, Baracat MC, Gustavo AR, *et al.* Androgen receptor gene polymorphism and polycystic ovary syndrome. Int J Gynaecol Obstet. 2013;120:115–118.
3. Aubuchon M, Legro RS. Polycystic ovary syndrome: Current infertility management. Clin Obstet Gynecol. 2011;54(4):675–684.
4. Diamanti-Kandarakis E, Kandarakis H, Legro RS. The role of genes and environment in the etiology of PCOS. Endocrine. 2006;30:19–26.
5. Colombo O,Pinelli G *et al.* Dietary intakes in infertile women a pilot study Nutr J 2009:8:53
6. Priyanka Kantivan goswami,Sunita Anubha Khale, Natural Remedies for Polycystic Ovarion Syndrome: A review,Int Journal pharma phytopharmacol. res 2012,1(60):396-402
7. Cheryce L, Catherine B. Lombard,Lisa J. Moren, Exercise Therapy in Polycystic Ovary Syndrome: A systematic Review, Human Reproductive updates, Vol 17,Issue 2, pages 171-183
8. Latha S, prasanna J,J hansi Rani, A-review on natural remedies for prevailing polycystic ovarion disorder, Indo American Journal Reserch,2015, issn 2231-6876, Pg no 3307
9. Natural Treatment for PCOS Get Well; 2014 September 19 Available FROM www. One medical. com/blog/live well/pcos treatment
10. Londonkar R *et al.*, Polycystic Ovary Syndrome (pcos)-A mini Review, Open Acess Journal of gynecology, issn 2474-9230, 2018, 3(1)
11. Allahbadia GN, Merchant R(2008), Polycystic ovary syndrome in the Indian Sub continent Seminar in Reproductive in women with Polycystic ovary Bjog 113(10)1148-1159
12. http//Jeanshaalis. org. au

Panacea Journal of Pharmacy and Pharmaceutical Sciences 2018:7(2);055-101
International Journal ISSN: 2349 7025

FORMULATION AND EVALUATION OF CIPROFLOXACIN FLOATING TABLET

Ashok Koshta*, Ankur Joshi, Narendra Vyas, Sapna Malviya, Anil Kharia

Modern Institute of Pharmaceutical Sciences, Indore, M.P., India

E-mail: ashokkoshta@gmail.com

ABSTRACT

Recent technological and scientific research has been constantly working towards the development of rate controlled drug delivery systems to overcome physiological adversities like gastric residence times and unpredictable gastric emptying times. Floating Drug Delivery Systems are of particular interest for drugs that are locally active and have narrow absorption window in stomach or upper small intestine, unstable in the intestinal or colonic environment. This study outlines the, preparation and evaluation of ciprofloxacin floating tablets. Since, Ciprofloxacin is characterized by short plasma half life therefore, developing a floating delivery system could improve clinical efficacy. Ciprofloxacin was characterized in preformulation studies for its solubility, organoleptic properties and drug excipient incompatibilities. Design of experiment was done by using factorial design and various formulae were prepared. Granules for tablets were prepared by appropriate method and were studied for Bulk Density, Tapped Density, Hausner's Ratio, Compressibility Index and Angle of Repose. After compression of the granules post compression studies were performed and studied for Hardness Thickness, Friability, Weight Variation, Floating Lag Time, Floating Time and Drug Release. The results of the study indicate that Weight Variation data of the prepared tablets indicated no significant difference in the weight of the individual tablet from the average value. Hardness of the tablets was observed in range of 1.263±0.07 to 1.184±0.05 kg/cm2. Thickness of the tablets was found in the range of 4.16±0.1 to 4.26±0.04 mm. Friability was found below 1%. The floating lag time was found to be in range of 15-22 sec. Total Floating Time was found to be in range of 6-7 H. Swelling Index was found to be between 78 to 124%. Drug Release of FT4 was found to be the good i.e. 94.524%. Floating lag time can be controlled by the hardness of the tablet. Floating lag time increases with increase in the hardness.

KEYWORDS: Floating Tablet, Ciprofloxacin, Gastro Retentive Drug Delivery System, *In vitro* Drug Release, Hydroxy Propyl Methyl Celulose, Poly Vinyl Pyrrolodone

INTRODUCTION

Gastro retentive drug delivery system

Gastro retentive drug delivery systems are those systems in which the tablet is forced to remain inside the stomach for long duration, thereby increasing the absorption of the poorly absorbed drug in stomach n upper part of intestine. [1,2]

Increasing the duration for which the drug or the tablet remains in the stomach increases the bioavailability of the drug, increases the drug released in stomach, an also increases the gastric residence time in the stomach. [3,4]

Floating drug delivery system

Floating drug delivery systems was first described by the scientist Davis in the year 1968. In this system the net density of the dosage for is less than that of the water. in other words the density is less than 1. Due to less density these systems remains buoyant in the fluid and float on the surface of the fluid. Floating drug delivery systems (FDDS) have bulk density lesser than gastric fluids, so they remain on the upper surface of the fluid in the stomach for longer duration of time. While the dosage is floating on the gastric fluids, the release of the drug is slow n steady as shown in fig. 1. However, there is a minimal level of floating force (F) which is also required to keep the tablet floating on the surface of the gastric fluid. [5,6,7]

Mechanism of floating system

The Floating System involves the use of buoyancy in order for the content to float in the gastric fluid these are a minimum volume of gastric fluid which must be there in order to achieve buoyancy and additionally the floating force is also required to keep the tablet floating. To measure the floating force, a apparatus is designed for determination of

resultant weight which is been reported in various research articles throughout. This apparatus works by measuring the force (F) with time which is required to maintain submerged objects. The apparatus helps in optimizing FDDS with respect to stability to their stability and durability of floating forces.[8,9]

$F = F_{buoyancy} - F_{gravity}$

$= (D_f - D_s)\, g\, v$

Where, F = Total vertical force, Df = fluid density, Ds = object density, v = volume

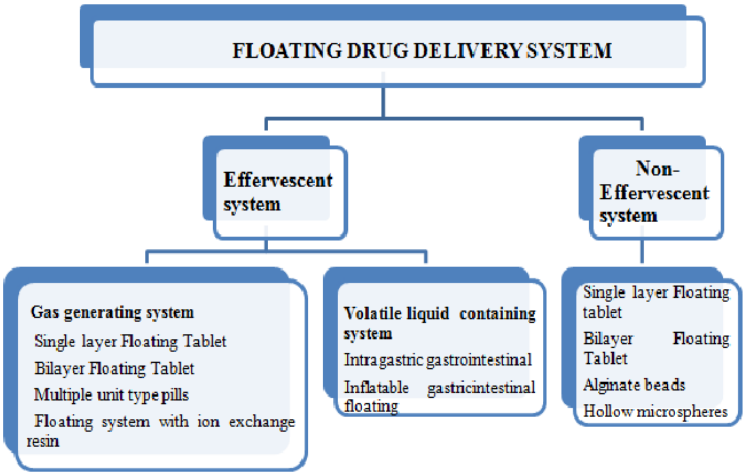

Figure 1. Classification of floating drug delivery systems

Description of drug

Molecular Formula: $C_{17}H_{18}F\,N_3O_3$

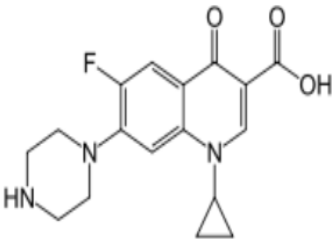

Figure 2. Chemical structure of ciprofloxacin

Mechanism of action

Ciprofloxacin is a broad-spectrum antibiotic active against both Grampositive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes which are essential for bacterial cell division.

Pharmacokinetics

Distribution: In blood serum, Ciprofloxacin is approximately 20-35% protein-bound. **Metabolism:** 30% drug is metabolized in liver.

Absorption: Rapidly absorbed after oral administration.

Elimination: Most of the Ciprofloxacin is excreted unchanged in the urine;

Recommended dose: 250 mg-700 mg (twice a day)

Uses

Ciprofloxacin is effective in a broad range of infections including some difficult to treat ones. Because of broad spectrum bacterial activity, oral efficacy and good tolerability, it is being extensively employed for blind therapy for any infection, more over it is widely used to treat urinary tract infections, Gonorrhea, Chancroid, Bacterial gastroenteritis, respiratory infections, tuberculosis and typhoid. [10]

EXPERIMENTAL WORK

Preformulation study

Various Preformulation Tests were carried out such as:

Organoleptic properties

The samples of Ciprofloxacin for colour, odour and taste were identified by visual inspection.

Melting point

The Melting point was determined by the capillary method using Melting point apparatus. Here, the capillary tube was filled by pressing the open end gently into Ciprofloxacin. When the drug was packed into the bottom of the tube, the tube will be placed into the slot behind the eye-piece on the Melt-temperature. Make sure the unit was plugged in and set to zero and then turn it on and near its reporting melting point then temperature knob adjust to down side.

Solubility study

The solubility of the drug was studied in various solvents like water, ethanol, methanol, chloroform etc. [11,12]

UV Spectrophotometry.

Determination of absorption maximum (λ max): The Ultraviolet absorption maximum was determined by scanning solution of Ciprofloxacin in absorption media in the range of 200 to 400 nm by Shimadzu-1800 UV/Visible Spectrophotometer.

Preparation of 0.1 N HCl (pH 1.2): 8.5 ml concentrated hydrochloric acid was taken and volume was made up to 1 liter with distilled water. The pH was adjusted to 1.2 with water prior to quantitative estimation.

Preparation of standard curve of Ciprofloxacin I. P in 0.1 N HCl (pH 1.2): 10 mg Ciprofloxacin I. P was dissolved in 100 ml of 0.1N HCl. From this stock solution different dilutions were prepared in the concentration range of 10, 20, 30, 40, 50 and 60 µg/ml in 10 ml volumetric flask and absorbance was taken at 230 nm.[13,14,15]

Drug excipients interaction studies

Fourier Transform Infrared Spectroscopy (FTIR) studies

The spectrum of Ciprofloxacin as determined by infrared absorption Spectrophotometry. The drug was directly place on the stub and determined by FT-IR which shows the characteristic absorption of various functional groups of drug in FT-I R spectra. The pure drug and physical mixtures were subjected for FTIR analysis. Spectra were analyzed for drug polymer interactions. [16,17]

Design and optimization of formula

The aim of present study is to make a Floating tablet of Ciprofloxacin using 2^2 factorial design. The 2^2 factorial design-based optimization was employed to investigate the effect of two independent process variables (factors), i.e., amount of Citric Acid and HPMC K15 on the dependent variables like Floating time and % Drug Release. Factorial design to achieve NLT 85% dissolution in 7 h. For optimization of ciprofloxacin floating tablets as per 2^2 Factorial design the Citric acid and HPMC K15 are considered as two Factors. Four ciprofloxacin floating tablet formulations employing selected combinations of the 2 Factors i.e., HPMC K15 and citric acid as per 2^2 Factorial designs were prepared. On increasing the concentration of HPMC K15 and decreasing the concentration of Citric Acid, An Increase

in % Drug Release was observed And an increase in Floating Time was observed. The results suggest that the concentration of both the factors have significant effect on the drug release and Floating Time.[18]

Precompression studies[19]

Bulk density

The bulk density of a powder is the ratio of the mass of an untapped powder and its volume including the contribution of the interparticulate void volume. It was measured by pouring the weigh powder in to a measuring cylinder and the volume was noted. It is expressed in gm/ml is given by:

LBD= M/Vo

Where,

M=the mass of powder, Vo= the bulk volume of powder.

Tapped density

It is a ratio of tapped mass upon tapped volume.

TBD=M/Vt

Where,

M= the mass of powder, Vt= the tapped volume of powder.

Angle of repose

This is maximum angle responsible between heap's surface and the horizontal plane is used to determine the flow property of granules. The angle of repose was determined by funnel method.

Tan ø = h/r

ø = tan-1 (h/r)

Where,

H= the height of pile of powder, R= the radius of pile of powder

Hausner's ratio

This value was calculated by making use of LBD and TBD

Hausner s Ratio= TBD/lBD

Where, TBD= tapped density of the powder LBD= bulk density of the powder.

Carr's index

Carr's Index is calculated using following formula.

Carrs Index= (TD-BD)/TD *100

Where: TD= Tapped Density BD= Bulk Density

Formulation of floating tablet

Procedure

1) Weighed quantity of Ciprofloxacin, HPMC, sodium bicarbonate, citric acid and MCC were taken according the formulae F1, F2, F3 and F4 (Table: 5.5) and sifted separately through mesh #44.

2) These materials were mixed in separate pestle mortar and were granulated by a solution of PVP k30 and isopropyl alcohol.

3) The granulated material was dried in a hot air oven at 40–45 degree Celsius.

4) The dried granules were sifted through mesh #30.

5) To these granules, weighed quantity of talc and magnesium stearate were added and mixed.

6) The blends were taken for compression activity on compression machine.

7) The tablets were compressed for formulae F1, F2, F3 and F4.

Table 1. Formula for floating tablet

S. NO	Ingredients	FT1	FT2	FT3	FT4
1	Ciprofloxacin	250 mg	250 mg	250 mg	250 mg
2	HPMC	70 mg	80 mg	90 mg	100 mg
3	Sod. Bicarbonate	100 mg	100 mg	100 mg	100 mg
4	Citric acid	40 mg	30 mg	20 mg	10 mg
5	MCC	15 mg	15 mg	15 mg	15 mg
6	PVP K30	20 mg	20 mg	20 mg	20 mg
7	Magnesium stearate	5 mg	5 mg	5 mg	5 mg
8	Talc	5 mg	5 mg	5 mg	5 mg
9	IPA	q. s	q. s	q. s	q. s

Evaluation of floating tablet [20]

Hardness

Hardness is amount of strength of tablet to be able to withstand various shocks during manufacturing to shipping. The limit for hardness of the tablet ranges from 3to 4 kg cm-1

Thickness

This test is used to calculate the thickness of the tablet. It was evaluated by Screw Gauge.

Friability

It was evaluated by Roche Friabilator. 6 tablets was weighed n placed in apparatus and was rotated for 4 min at 25rpm the these were reweighed and % friability was calculated using following formula. The value is expressed as a percentage. General acceptance limit is.5-1%

Friability = Initial weight-final weight/Initial weight * 100

Weight variation

This test is used to check the uniformity of weight.

Floating lag time

Three individual tablets from each formulation were put in an individual flask containin 400 ml of 0.1(N) HCL solutions. Then note time in minutes for each tablets to go from the bottom to the top of the flask is called as floating lag time was measured.

Floating time

Three individual tablets from each formulation were put in an individual flask containing 400 ml of 0.1(N) HCL solutions. Then note the time for which tablets float on the surface of

water.

Swelling index (SI)

The swelling Index of the tablets was determined by following procedure.

1. In order to calculate the swelling index, tablets were initially weighed, kept in 100 ml of 0.1N HCl solution and were drawn out of the solution at determined time points, dried and their weights were taken.

2. Swelling indices was calculated by the formula:

% SI= (W2-W1)/W1*100

In vitro release study of tablet [21]

Drug dissolution testing is routinely used to provide critical *in vitro* drug release information for both quality control purposes, *In vitro* release studies were carried out by using United States of Pharmacopoeia (USP) Dissolution Testing Apparatus II (VEEGO, VDA-6DR). The 900 ml of the media (0.1N HCl) is taken in the flask by using paddle type apparatus at 50 rpm at 37 ^{0}C various times interval the 5 ml of sample was withdrawn and sink condition was maintained and all the samples were filtered and 1 ml solution is pipette out and volume is made by appropriate solvent and was analyzed by U. V visible spectrophotometer.

RESULT

Preformulation studies

Organoleptic properties

The sample of Ciprofloxacin was identified for colour and odour which were found to be white and odourless respectively.

Melting point

The melting point of Ciprofloxacin I. P was found to be 254 °c. and the drug was found to be in the pure form.

Solubility studies

The solubility of the drug sample was determined by accurately weight 10 mg of Ciprofloxacin I. P was added in 6 test tubes and was added in aqueous and non aqueous solvents and solution was kept for 24 h and then samples were analyzed by U. V visible spectrophotometry and were found to be soluble in polar and were found to be insoluble in non polar solvents.

UV Visible spectroscopy studies

Table 2. Spectrophotometric data for standard curve of ciprofloxacin (0.1N HCl)

S. No.	Conc. (µg/ml)	Absorbance at λmax 282 nm
1	10	0.049
2	20	0.162
3	30	0.247
4	40	0.316
5	50	0.399
6	60	0.428

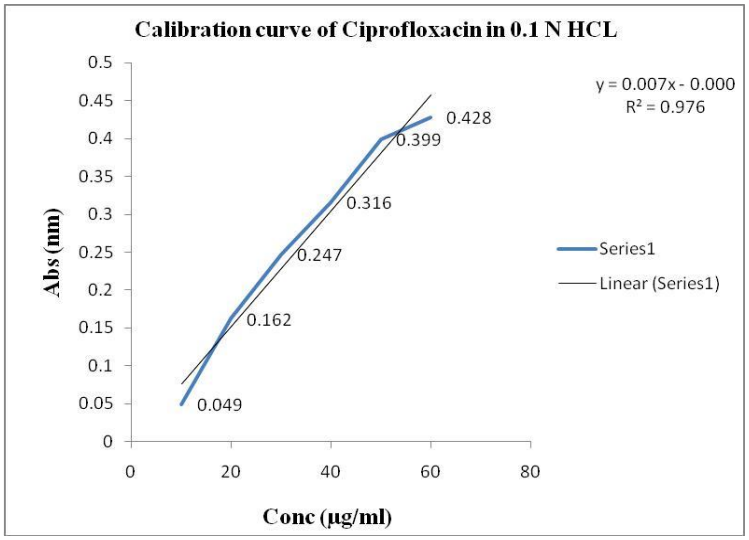

Figure 3. Standard curve of ciprofloxacin in 0.1 N HCL at 282 nm

Drug–excipients interaction studies

Fourier Transform Infrared Spectroscopy (FTIR) studies

The characteristics peaks were determined by FTIR spectra, which show purity of drug. If sample does not contain characteristics peaks of compound than it shows the impurity of sample.

Figure 4. FTIR spectra of ciprofloxacin

FTIR show characteristic peaks of drug which was similar to that of standard. It was the Test for identification of drug. This test confirms the presence of various groups in the sample and confirms that it was Ciprofloxacin.

Precompression studies

Evaluation of floating tablets

Drug release of tablets

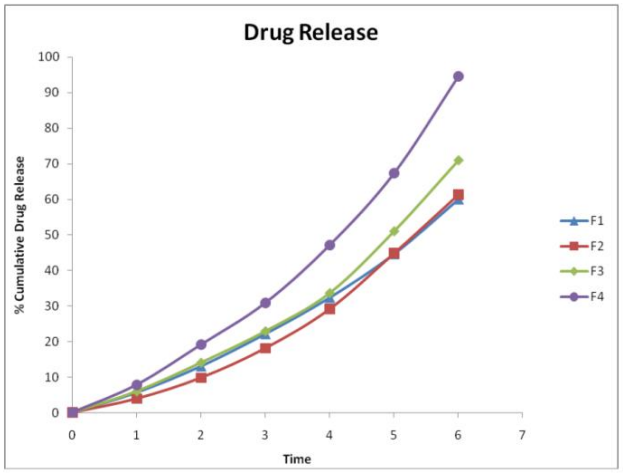

Figure 5. *In vitro* drug release profile of ciprofloxacin tablets for various tablet formulation (FT1 to FT4)

Dissolution was carried out in USP apparatus 2, paddle type, six bucket dissolution apparatus. Formulated (F1, F2, F3 and F4) tablets were fixed with sinkers and put in the buckets of the dissolution apparatus filled with 0.1 N HCl upto 900 ml maintained at a temperature of 37±0.5 **o** C and paddle rotation speed at 50 rpm. Samples were withdrawn at time points of 1, 2, 3, 4, 5 and 6 h and analyzed in UV-spectrophotometer (Schimadzu UV-1800) at lambda max of 282 nm. The values of absorbance obtained were used to calculate the amount of drug release.

Release Kinetics for Optimized Formulation (FT4):

1. Zero Order Release Kinetics:

For Calculation of zero order release kinetics, a Plot is made between Percentage

2. First Order Release Kinetics

For Calculation of first order release kinetics, a Plot is made between Log Cumulative of Percentage Drug Remaining Vs. Time.

4. Higuchi Model Release Kinetics

For Calculation of Higuchi Release Kinetics, a Plot is made between Cumulative Percentage Drug Release Vs. Square Root Of Time.

5. Korsmeyer Pappas Release Kinetics

For Calculation of Korsmeyer Pappas Release Kinetics, a Plot is made between Log Cumulative Percentage Drug Release Vs. Log Time.

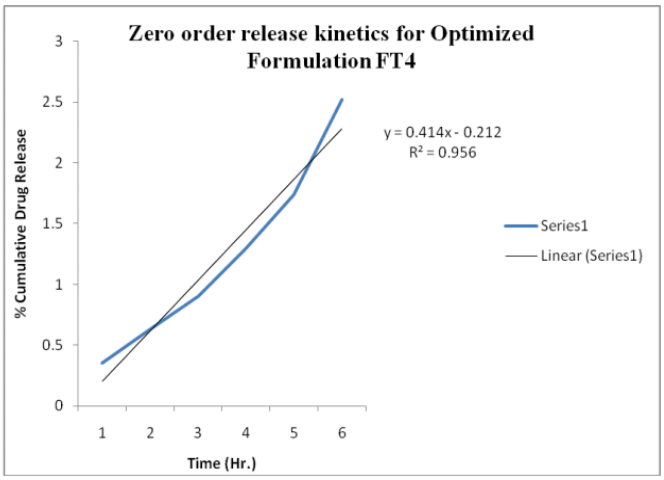

Figure 6. Zero order release kinetic plot of optimized formulation (FT4)

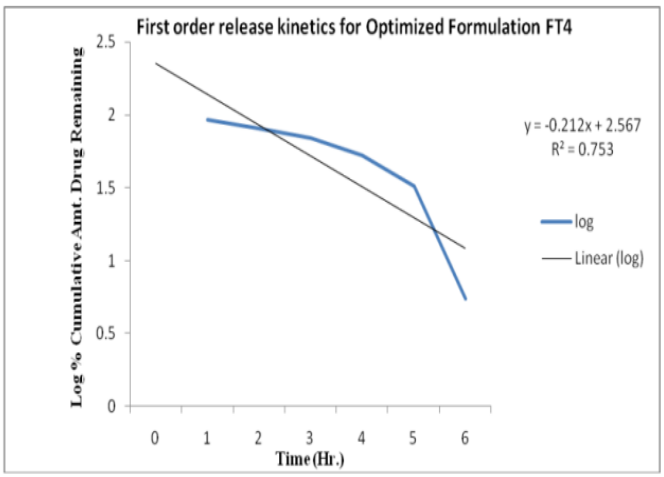

Figure 7. First order release kinetic plot of optimized formulation (FT4)

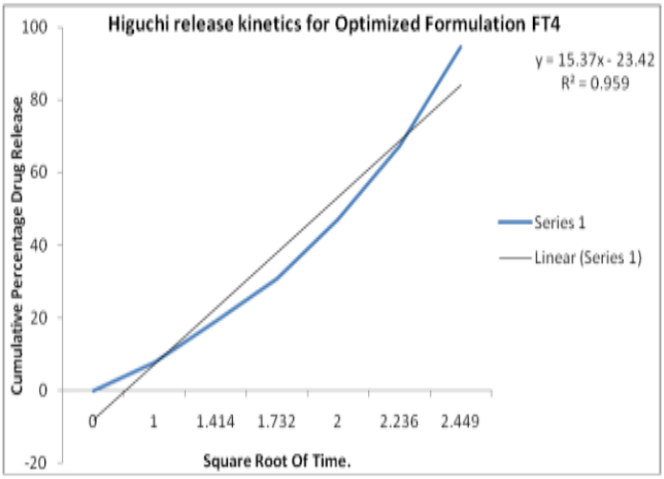

Figure 8. Higuchi kinetic plot of optimized formulation (FT4)

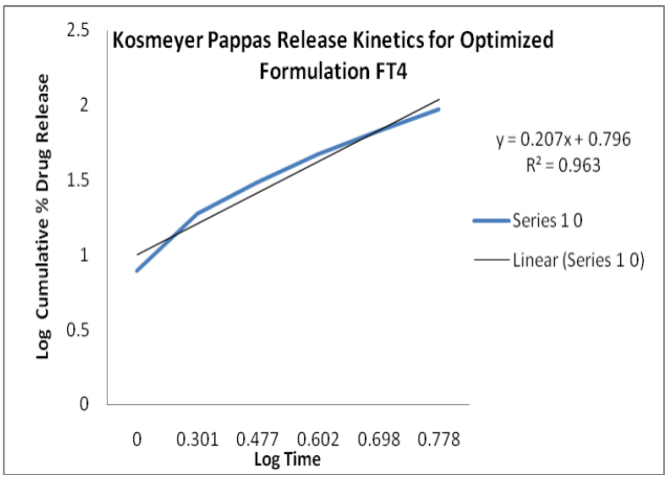

Figure 9. Kosmeyer Pappas plot of optimized formulation (FT4)

The Higuchi model and Korsmeyer Peppas model were found to be best fitted release kinetic model as their Regression Coefficient (R2) were found to be in the range for the Drug Release of Ciprofloxacin Floating Tablet.

Figure 10. Ciprofloxacin floating tablet

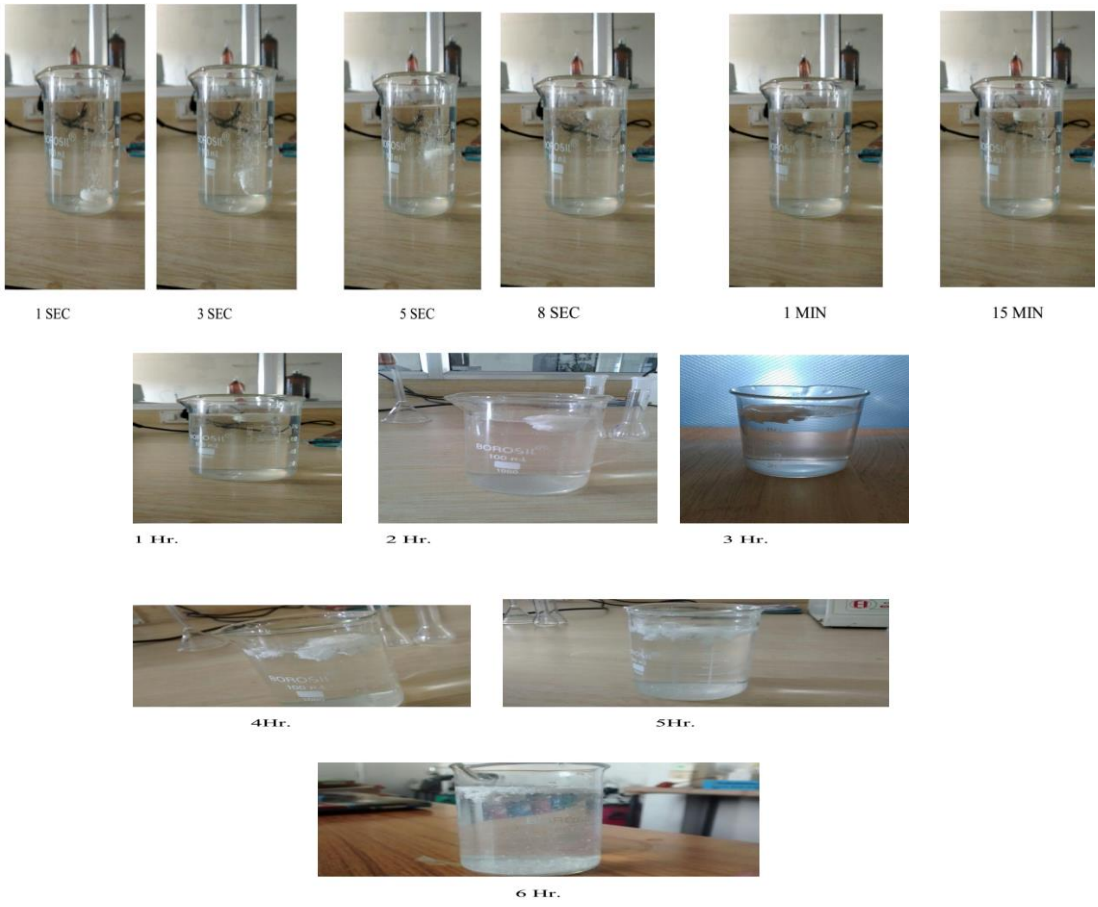

Figure 11. Pictures showing floating time of tablet

CONCLUSION

The Main objective of the study was to prepare and evaluate ciprofloxacin floating tablet. An attempt was made to prepare. The Drug Ciprofloxacin was selected after looking in various research studies of Floating Tablet. First organoleptic properties of drug was studied. Then Melting point of the drug was identified by Capillary method and it was found to be 254 °C.

Solubility of Ciprofloxacin as determined in various aqueous and non-aqueous solvents. The drug was found to be soluble in Water, Ethanol and Methanol and Insoluble in chloroform.

Calibration curve of the drug were prepared in 0.1 N HCL with the help of UV spectrophotometer. The method used for the estimation of drug followed Beer Lambert's law in the concentration range 2 to 20 µg/ml with good accuracy, which is evident from regression coefficient obtained for each calibration curve.

Drug Excipients Studies was determined by infrared absorption Spectrophotometry. The characteristics peaks were determined by FTIR spectra, which show purity of drug. FTIR show characteristic peaks of drug which was similar to that of standard. It was the test for identification of drug. This test confirms the presence of various groups in the sample and confirms that it was Ciprofloxacin.

A new formula was developed using factorial design n the various sub formulas was prepared accordingly. Then the Precompression Studies which included Bulk Density, Tapped Density, Hausner's Ratio, Compressibility Index and Angle of Repose was then studied accordingly and data so obtained which is given in detail in results.

The tablet was prepared using appropriate procedure n equipments and then Post Compression Studies was performed accordingly. The post compression studies included Hardness Thickness, Friability, Weight Variation, Floating Lag Time, Floating Time, Drug Release.

The results of our study clearly indicate that Weight Variation data of the prepared tablets indicated no significant difference in the weight of the individual tablet from the average value. Hardness of the prepared tablets was observed in range of 1.263±0.07 to 1.184±0.05 kg/cm2. Thickness of all the tablets was found in the range of 4.16±0.1 to 4.26±0.04 mm. Friability was found below 1%. The floating lag time was found to be in range of 15-22 sec.

Total Floating Time was found to be in range of 6-7 H. Swelling Index was found to be between 78 to 124%. Drug Release Of FT4 was found to be the good i.e. 94.524%.

From results it concludes that the floating lag time increased as hardness increased and F4 had better controlled release than the other formulations. So, formulation F4 provides a better option for Controlled release action and improved bioavailability of Ciprofloxacin Hydrochloride.

On the basis of present study it was concluded that floating tablets of ciprofloxacin hydrochloride can increase the gastric residence time as well as bioavailability and thus better patient compliance can be achieved.

REFERENCES

1. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert opinion on drug delivery. 2006 Mar 1;3(2):217-33.
2. Garg RG, Gupta GD. Progress in controlled gastroretentive delivery systems. Tropical journal of pharmaceutical research. 2008;7(3):1055-66.
3. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. Aaps PharmSciTech. 2005 Sep 1;6(3):E372-90.
4. Vedha H, Chaudhary J. The recent developments on gastric floating drug delivery system: An overview. Int j pharm tech res. 2010;1(2):524-34.
5. Gupta P, Vermani K, Garg S. Hydrogels: from controlled release to pH-responsive drug delivery. Drug discovery today. 2002 May 15;7(10):569-79.
6. Garg S, Sharma S. Gastroretentive drug delivery systems. Business Briefing: Pharmatech. 2003 May; 5:160-6.
7. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. Research journal of pharmacy and technology. 2008 Oct; 1(4):345-8.

8. Rubinstein A, Friend DR. Specific delivery to the gastrointestinal tract. polymeric site-specific Pharmacotherapy, Wiley, Chichester. 1994:282-3.
9. Jaimini M, Rana AC, Tanwar YS. Formulation and evaluation of famotidine floating tablets. Current drug delivery. 2007 Jan 1;4(1):51-5.
10. Tripathi, K. D. Essentials of medical pharmacology, 6th ed., Jaypee brother's medical, Publishers, 2008; pg 686-689.
11. Iannuccelli V, Coppi G, Bernabei MT, Cameroni R. Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. International journal of pharmaceutics. 1998 Nov 15;174(1-2):47-54.
12. Wu W, Zhou Q, Zhang HB, Ma GD, Fu CD. Studies on nimodipine sustained-release tablet capable of floating on gastric fluid with prolonged gastric resident time. Yao xue xue bao= Acta pharmaceutica Sinica. 1997 Oct; 32(10):786-90.
13. Timmermans J, Moes AJ. How well do floating dosage forms float?. International journal of pharmaceutics. 1990 Jul 31;62(2-3):207-16.
14. Kamalakkannan V, Puratchikody A, Prasanth VV, Masilamani K. Enhancement of Drugs Bioavailability by Floating Drug Delivery System-A Review. International Journal of Drug Delivery. 2011 Oct 1;3(4):558.
15. Kamalakkannan V, Puratchikody A, Prasanth VV, Masilamani K. Enhancement of Drugs Bioavailability by Floating Drug Delivery System-A Review. International Journal of Drug Delivery. 2011 Oct 1;3(4):558.
16. Pawar HA, Dhavale R. Development and evaluation of gastroretentive floating tablets of an antidepressant drug by thermoplastic granulation technique. Beni-Suef University Journal of Basic and Applied Sciences. 2014 Jun 1;3(2):122-32.
17. Eberle VA, Schoelkopf J, Gane PA, Alles R, Huwyler J, Puchkov M. Floating gastroretentive drug delivery systems: Comparison of experimental and simulated dissolution profiles and floatation behavior. European journal of pharmaceutical sciences. 2014 Jul 16;58:34-43.
18. Shakya R, Thapa P, Saha RN. *In vitro* and *in vivo* evaluation of gastroretentive floating drug delivery system of ofloxacin. asian journal of pharmaceutical sciences. 2013 Jun 1;8(3):191-8.
19. Yin L, Qin C, Chen K, Zhu C, Cao H, Zhou J, He W, Zhang Q. Gastro-floating tablets of cephalexin: preparation and *in vitro*/*in vivo* evaluation. International journal of pharmaceutics. 2013 Aug 16;452(1-2):241-8.
20. Baru CR, Vidyadhara S, Rao KR, Umashankar KV. Formulation and evaluation of ibruprofen floating tablets. International Journal of pharmaceutical, chemical and biological sciences. 2012;2(4):472-81.
21. Chaurasia DE, Kaushik K, Bhardwaj P, Chaurasia H, Jain SK, Shobhna SI. Development and *in vitro* characterization of floating microspheres bearing tramadol HCl. Acta Pol Pharm. 2011 Sep 1;68:795-801.
22. Kumar PD, Rathnam G, Prakash CR, Saravanan G, Karthick V, Selvam TP. Formulation and characterization of bilayer floating tablets of ranitidine. Rasayan J chem. 2010;3(2):368-74.
23. Barmpalexis P, Kachrimanis K, Georgarakis E. Solid dispersions in the development of a nimodipine floating tablet formulation and optimization by artificial neural networks and genetic programming. European Journal of Pharmaceutics and Biopharmaceutics. 2011 Jan 1; 77(1):122-31.

MULTI TARGETED DRUG DISCOVERY (MTDD)

Yash Bhandari*, Shweta Mishra

Sri Aurobindo Institute of Pharmacy, Ujjain Highway, Indore-453111, M.P., India

E-mail: yb1231998@gmail.com

ABSTRACT

MTDD is the method to find drug leads that simultaneously interact with multiple targets. The use of drugs to target different, often unrelated, pathways or multiple biological targets, with the expectation of synergistic effects and low toxicity than combinational therapy, becomes an approach of increasing interest. Therefore, the discovery of multi-targeted agents through rational design has been a subject of growing interest in anticancer drug discovery. Due to the multi-factorial nature of most diseases, a selective compound for a single target rarely achieves the desired effect and is often combined with standard treatments or other novel targeted agents to improve effectiveness. Combination

therapy is an important treatment modality in many disease settings, including hypertension, dyslipidemia, tuberculosis, human immunodeficiency virus (HIV) infections, and cancer. For designing the drugs in combination they should be individually active, should have different mechanisms of action, should have non-overlapping mechanism of resistance, should have different toxicities and should be administered at maximum doses and schedules. There are various *insilico*methods such as molecular docking, Pharmacophore mapping, QSAR, Machine learning methods, scaffold hopping, ligand-based or fragment based strategy for designing the MTDD. The main challenge in optimizing the MTDD agents to maintain the balance between the physicochemical property and pharmacokinetic profile. This article deals with the rationale for combination therapies, the strength and weakness of selective and multi targeted agents as combination used for treatment.

KEYWORDS: MTDD, Combinational therapy, toxicity, biological effect, targets.

INTRODUCTION

MTDD is the type of target discovery in which there is more than one target site which gives primary action and secondary action on the multiple targets. The main aspect behind the MTDD is to have more potency of the drug and low toxicity.

The transition of the single target to multi target concept by the drug design is said to be multi target discovery (MTDD).

There are generally two types of target networks:

(a) Drug-drug Network
(b) Target-target Network.

Figure 1. A single drug binding at three different binding sites A, B, and C

Generally the Computer Aided Drug Design (CADD) method is used in the MTDD which are as follows-

(a) QSAR (Quantitative Structure Activity Relationship)
(b) Pharmacophore Modelling

Using the two approaches SAR (Structure Activity Relationship) is designed and on the basis of this the designing of compounds can be done such that it can simultaneously bind at multiple sites.

(c) Molecular Docking.

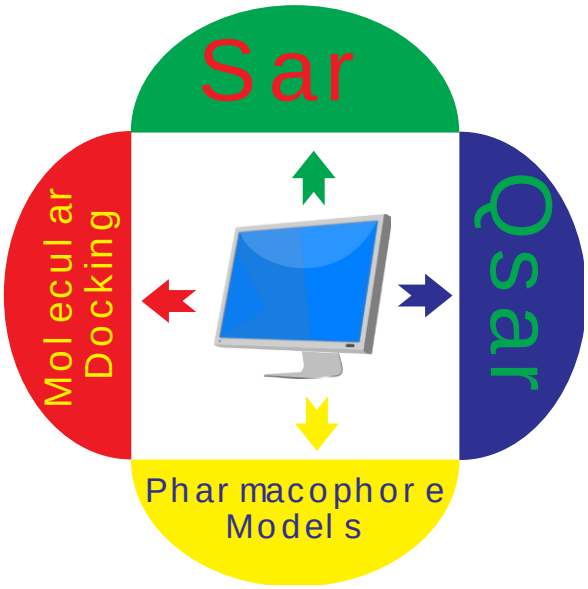

Figure 2. Different methods used in MTDD

(a) QSAR (Quantitative Structure Activity Relationship):-These models are regression or classification models used in chemical and biological sciences and engineering. QSAR has the form of a mathematical model:
Activity= f (physiochemical properties and/or structural properties)+error
(b) Pharmacophore Modelling: -An ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response.
(c) SAR (Structure Activity Relationship):-It is the relationship between the chemical or 3D structure of a molecule and its biological activity. The analysis of SAR enables the determination of the chemical group responsible for evoking a target biological effect in the organism.
(d) Molecular Docking:-It is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure.

After the designing of compounds using different PDB and reference ligands we will compare the dock score of our compounds with the reference compound and then analyze the dock pose so that the false results can be eliminated.

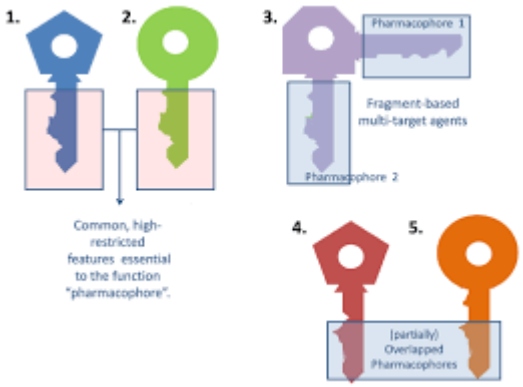

Figure 3. Pharmacophore designing concepts

Principles

The main principle of MTDD in the anti-neoplastic or anti-cancer drug are as follows-

1. The activity of all the drugs must be as a single agents.
2. The non-overlapping toxicity should be chosen for drugs.

3. The synergistic effect and mechanism of action of the drug should be chosen.
4. The pattern of resistance should be chosen for the drugs.
5. The administration of the drug should be by optimum dose and schedule.

Some of the drugs discovered by the MTDD concept were Captopril (ACE inhibitor), Rosiglitazone (PPAR-gamma inhibitor), Rivastigmine (AChE inhibitor), Fluoxetine (SERT inhibitor), Haloperidol (anti-dopaminergic), Celecoxib (COX-2 inhibitor) and the 7th largest selling anti-cancer drug Bevacizumab.

The lead challenge in multi-target drug discovery is the violation of lippinski rule, the high molecular weight and risk of getting metabolized before producing activity.

Generally these are the classof drugshaving higher molecular size:-

1. Hypertension
2. Dyslipidemia
3. HIV Infections
4. Tuberculosis.

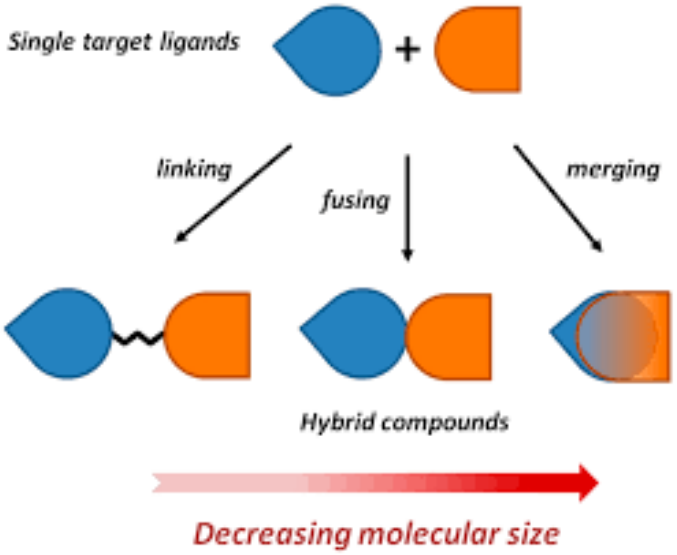

Figure 4. Framework combination

To overcome from the problem of higher molecular size we use hybrid molecule formation which utilizes following methods:-

a. Linking
b. Merging
c. Fusing

The binding of single target ligand to form a hybrid compounds.

In linked designed multiple ligands (DMLs), the molecular frameworks are not at all integrated and there is a distinct linker group between the two components that is not found in either of the selective ligands. This linker is usually intended to be metabolically stable so that the single compound is capable of interacting with both targets, albeit different ends of the molecule may be responsible for the activity at the different targets. Some linked DMs contain a cleavable linker that is designed to be metabolized to release two ligands that interact independently with each target.

When the resistance of the drug on single target site shows no side effects but when no resistance occur gives therapeutic effects. In case of multi target site the resistance at primary site gives no side effects, and when no resistance occur gives therapeutic effects, and the secondary site have the therapeutic effect too.

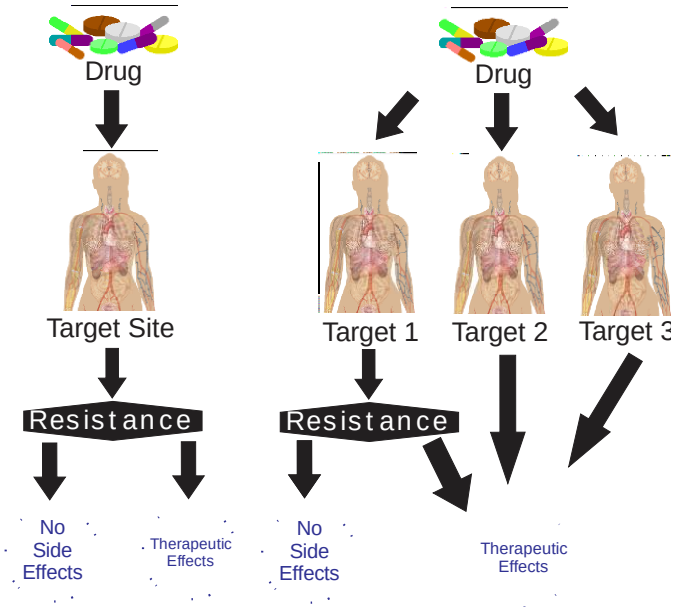

Figure 5. Resistance and biological activity with relation to MTDD

CONCLUSION

The MTDD is totally based on the action of the drug on more than one site with the more therapeutic effect as compare to single target. The need of the MTDD is to overcome from the problem of high toxicity of the drugs having higher molecular size and less absorption of the drug too. The potency of the drug should be enhanced by formulating the drug in form of MTDD.

REFERENCES

1. Morphy J. R.; Harris C. J., Designing Multi Target Drugs, RSC Publishing House, 2012, 141-152, http://dx. doi. org/10.1039/9781849734912
2. http://www. sciencedirect. com>pii/S135964461000111X
3. Morris GM, molecular docking, methods molecular biology, molecular modeling of proteins, 2008, Vol. 443, 365-382. http://www. ncbi. nlm. nih. gov>pubmed/18446297
4. http://en. m. wikipedia. org. in
5. Morphy J. R, Camille Georges Wermuth, David Aldous, Pierre Raboisson, Didier Rognan, Practice of medicinal chemistry, 2014, 4th ed., 549-561.