International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1407-1412 www.ijprajournal.com ISSN: 2456-4494

Formulation And Evaluation Of Hydroxyzine Hydrochloride Sustain Release Tablet

* Divya Maita[1], Jyoti Gupta[2]
[1]Student, IEC School of Pharmacy, IEC University, Distt. Solan, Baddi, H.P., India.
[2]HOD, IEC School of Pharmacy, IEC University, Distt. Solan, Baddi, H.P., India.

Submitted: 05-08-2022 Accepted: 14-08-2022

ABSTRACT:
The aim of this research was formulation of hydroxyzine hydrochloride sustain release matrix tablet and studying the influence of different types and concentrations of polymers on release of drug . Five formulations were manually designed using different properties and amount of polymer . The formulation of matrix tablet F1-F4 were composed of different polymers such as Ethylcellulose (EC-10cps) , carboxymethyl cellulose (cmc) , hydroxypropyl cellulose (HPMC-K 15 M) , sodium lauryl sulphate (SLS) , Whereas F5 standard formulation were composed of two polymers hydroxypropyl cellulose (HPMC – K 4 MCR) and hydroxypropyl cellulose (HPMC-K 15 M) and dissolution test were performed in phosphate buffer of pH 7.4 .
KEYWORDS: Ethylcellulose , HPMC , Sodium lauryl Sulphate .

I. INTRODUCTION:

Hydroxyzine is an antihistamine that reduces the effects of natural chemical histamine in the body. Histamine can produce symptoms of itching, or hives on the skin. Hydroxyzine used to treat allergic skin reactions such as hives or contact dermatitis. However, Hydroxyzine is a short acting anti-histamine drug with the duration of action of 3 -4 hours, resulting in frequent dosing of four times a day.

To overcome the limitations, the present study is focused on development of sustain release formulation, which are able to maintain steady state drug plasma levels for extended periods of time as a result of which the variations of the drug levels in the blood and drug-related side effects are minimized. Sustained release preparations are useful to reduce the dosage frequency to improve patient compliance[1]

Histamine is a primary amine that in humans is synthesized from histidine in the Golgi apparatus and stored in the secretory granules of both mast cells (±v3 pg/cell) basophils, (±1 pg/cell) as well as in the histaminergic nerves. It is among a heterogeneous group of mediators including kinins, prostaglandins, leukotrienes, lipoxins and platelet-activating factors, and the release from basophils and mast cells can be accomplished by means of immunologic and non-immunologic stimuli. In 1910, histamine was reported by Dale & Laidlaw to exert activity as a uterine stimulant in ergot extracts. These investigators found the effects of intravenous administration of histamine to mimic those of anaphylaxis, suggesting a role as a significant mediator of allergic reactions. [2-3] The role of histamine as a critical mediator of allergic reactions was demonstrated by Bouvet &Staub, who observed anaphylaxis protection in guinea pigs who had received compounds with antihistaminic activity. In allergic patients, exposure to specific antigens leads to a local or systemic increase in histamine concentrations.Mast cells are present such locations as lung parenchyma and skin tissues, and can be stimulated to release histamine, while histamine-secreting basophils are attracted by several chemokines from peripheral blood to the sites ofallergic inflammation. Additionally, histamine has been shown to affect chronic inflammation and regulate several essential events in theimmune response, recruiting major effector cells into tissue sites and affecting their maturation, activation, polarization and effector functions, which may lead to chronic inflammation. Histamine also influences the cytokine network in allergic inflammation, affecting both cytokine production and modulation of cytokine synthesis due to immunologic stimuli. (Lagier et al., 1997)demonstrated that the release of IL-4 and IFN-γ from T-cells is differentially modulated by histamine. Other effects of histamine include activity on human monocytes, resulting in inhibition of monocyte production of TNF-α and IL-12 and induction of IL10 and IL-18 synthesis, while also enhancing IL-1-induced production of IL-6. Histamine has also been found to inhibit IFN-γ, TNF-α and IL-12 production while enhancing

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1407-1412 www.ijprajournal.com ISSN: 2456-4494

that of IL-10 in peripheral blood mononuclear cells that have been activated by LPS or mitogens. The allergic process is caused by an immune response to a normally innocuous substance, and consists of an early and late phase. The early phase reactions are induced primarily from mast cells in response to a particular antigen, following the attachment of a free-floating IgE molecule specific to the antigen to the surface receptors on mast cells. Antigen binding to the mast cell-IgE complex triggers an immune response in the form of histamine release. [4-5]

A retrospective case study was performed using the clinical charts of patients diagnosed with atopic dermatitis, dermatitis, urticaria, and other allergic conditions, treated with Hydroxyzine hydrochloride from the period of 2001 to 2003. Patients of both sexes were identified by the diagnosis and treatment prescribed, and having returned for at least one post-treatment visit. A total of 41 patients were identified who fulfilled the criteria for this safety and efficacy analysis of Hydroxyzine hydrochloride. The results suggest that Hydroxyzine is an effective antihistaminic agent in the treatment of numerous allergic and inflammatory conditions. The pro-inflammatory actions of histamine include vasoactivity, constriction of smooth muscles and stimulation of nociceptive itch nerves, in addition to other proinflammatory actions. Clinical allergy symptoms are caused by histamine binding specific cell receptors. Histamine release may also lead to the activation of eosinophils and neutrophils, while histamine may also play a role as a chemo attractant for these cells. Histamine also increases IL-8 levels and stimulates leukocyte rolling on endothelial cells.[2]

THE RATIONALE OF THE STUDY:

- To extend the duration of action of the drug
- To reduce the frequency of dosing
- To minimize the fluctuations in plasma level
- Improved drug utilization
- To reduce the adverse effects by reducing the overall dose[15,16]

II. MATERIALS AND METHODS:

Materials :

Hydroxyzine was procured from chempfinechemicals , India . Hydroxypropyl methylcellulose (HPMC-K 100 M) was procured from SUNHERE , china . Ethlycellulose (EC-10cps) was procured from chemist group , Peru . Hydroxypropyle cellulose high viscosity was procured from Nippon Soda –Japan .All other materials used were of pharmaceutical grades .

Methods :

Preperation of granules by wet granulation method :

Hydroxyzine Hydrochloride IP ,Methocel K4M CR, Methocel K 15 M , Lactose monohydrate , Hydroxypropyl Cellulose were mixed using Isopropyl alcohol and purified water (binder). The granules were prepared by passing the dough from 40 no. screen . The granules were dried in FBD(Allince) for 90 min. Then Silicon Dioxide (glidant) and Magnesium Stearate IP (lubricant) mixed with the prepared granules. The granules were then evaluated and compressed using sejong (punching machine) . The quantity of ingredients is given in table 3.

Coating of tablets :

Barrier coating ;The coating solution would be prepared by dissolving acetone in isopropyl alcohol Then the solution is sprayed over the tablet bed using Ganson(coater) with 1.0 mm nozzle size . The tablets would be allowed to dry using hot air flow maintained at 40 ˚C for 50 to 60 min.

Film Coating :The coating solution would be prepared by dissolving HPMC in Purified water Then the solution is sprayed over the tablet bed using Ganson(coater) with 1.0 mm nozzle size . The tablets would be allowed to dry using hot air flow maintained at 45˚C for 30 min.

Composition	Formulation				
	F1	F2	F3	F4	F5
Hydroxyzine	200	200	200	200	200
HPMC –K 4 M CR	120	90	100		
HPMC –K 15 M		60		40	
Lactose monohydrate (mg)	70	40	50	90	160
Hydroxypropyl cellulose (mg)			40	150	
Carboxymethyl cellulose (cmc)					
Sodium lauryl sulphate (SLS)	40	40	40	40	40

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1407-1412 www.ijprajournal.com ISSN: 2456-4494

Total Weight Tablet (mg)	**600**	**600**	**600**	**600**	**600**

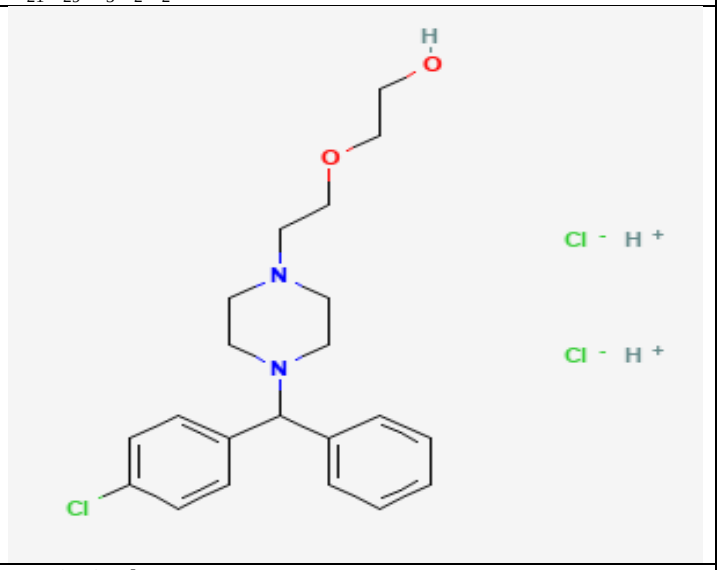
Tabel 1. Compositions of different hydroxyzine SR formulations.

ANTIHISTAMINES:

Antihistamines are a pharmaceutical class of drugs that act to treat histamine-mediated conditions. There are two main classes of histamine receptors: H_1 receptors and H_2 receptors. Antihistamine drugs that bind to H_1 receptors are generally used to treat allergies and allergic rhinitis. Drugs that bind to H_2 receptors treat upper gastrointestinal conditions that are caused by excessive stomach acid[3]

H_1 antihistamines are further classified according to first and second-generation agents. First-generation H_1 antihistamines more easily cross the blood-brain barrier into the central nervous system (CNS), whereas second-generation H-1 antihistamines do not. The first-generation drugs will bind to both central and peripheral H_1 receptors, whereas second-generation drugs selectively bind to peripheral H_1 receptors; this leads to different therapeutic and side effect profiles. [8-10]

Hydroxyzine is a first-generation antihistamine of the diphenylmethane and piperazine classes. It was first synthesized by Union ChimiqueBelge in 1956. Due to its antagonistic effects on several receptor systems in the brain, Hydroxyzine has strong anxiolytic and mild antiobsessive as well as antipsychotic properties Because of its antihistamine effects it can also be used for the treatment of severe cases of itching, hyperalgesia and motion sickness-induced nausea. [11]

Volume of distribution:	16.0 ± 3.0 L/kg
Generic name:	Hydroxyzine (Hydroxyzine Hydrochloride)
Type:	Small molecule
Molecular formula:	$C_{21}H_{29}Cl_3N_2O_2$
Structure:	
Molecular weight:	447.8 g/mol
IUPAC name:	2-[2-[4-[(4-chlorophenyl)-phenylmethyl]piperazin-1-yl]ethoxy]ethanol;hydron;dichloride
Protein binding:	Hydroxyzine has been shown to bind to human albumin in vitro, but the extent of protein binding in plasma has not been evaluated.
Metabolism:	Hydroxyzine is metabolized in the liver by CYP3A4 and CYP3A5.
Route of elimination:	Approximately 70% of Hydroxyzine 's active metabolite, cetirizine, is excreted unchanged in the urine.
Half-life:	The half-life of Hydroxyzine is reportedly 14-25 hours, and appears to be, on average, shorter in children (~7.1 hours) than

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1407-1412 www.ijprajournal.com ISSN: 2456-4494

	in adults (~20 hours).
Clearance:	Clearance of Hydroxyzine has been reported to be 31.1 ± 11.1 mL/min/kg in children and 9.8 ± 3.3 mL/min/kg in adults.
Onset of action	15 – 30 min. (Fast Onset)
Duration of action	3 – 4 hrs. (Short acting antihistamine)

Table 2: Physicochemical properties of Hydroxyzine[12]

MECHANISM OF ACTION OF HYDROXYZINE :

(an endogenous chemical messenger) induces an increased level of vascular permeability, which leads to fluid moving from capillaries into the surrounding tissues. The overall outcome of this is increased swelling and dilation of vessels as shown in below figure 1

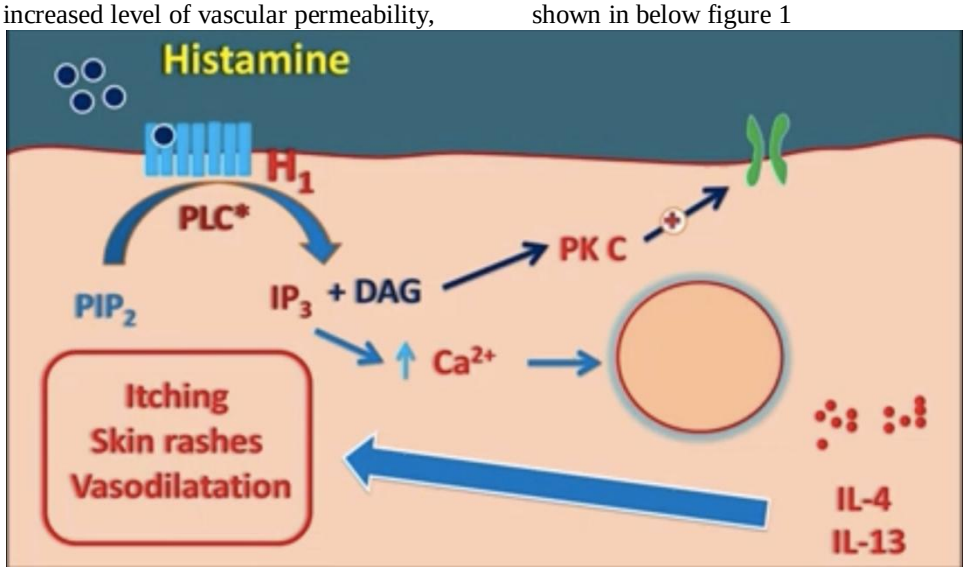


Figure 1: Illustrating the etiology of allergic reaction due to Histamine

Antihistamines stop this effect by acting as antagonists at the H_1 receptors. The clinical benefit is a reduction in allergy symptoms and any related symptoms, shown in below figure 2. [16-17]

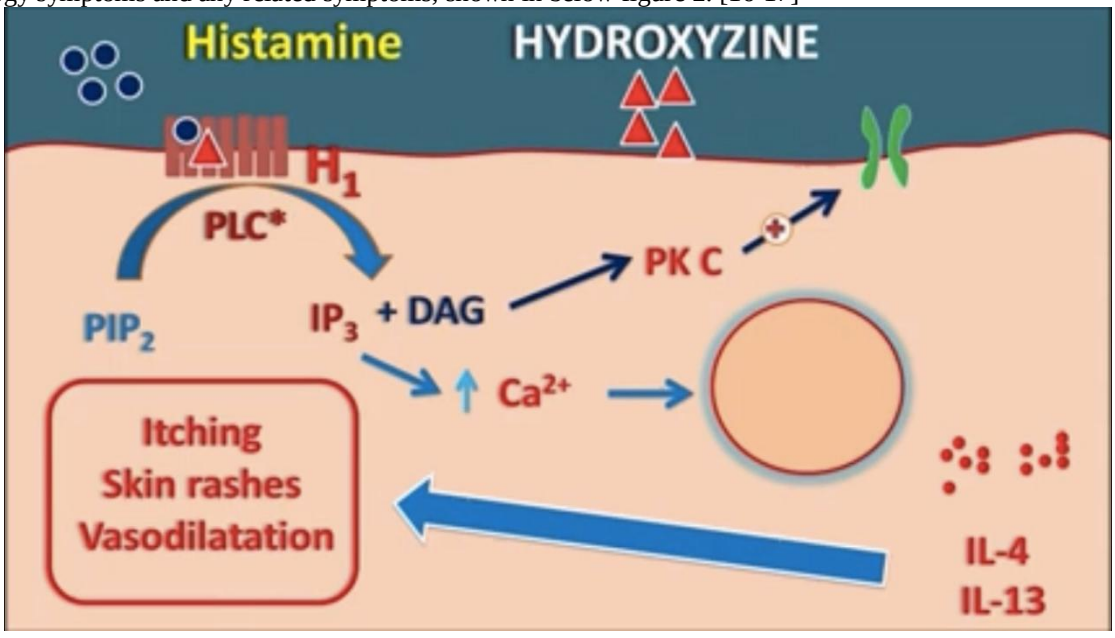


Figure 2: Illustrating the competitive binding of Hydroxyzine with H_1 receptors

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1407-1412 www.ijprajournal.com ISSN: 2456-4494

III. RESULT AND DISCUSSION :

Formulations	Weight Variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friblity (%)	Assay (%)
F1	596.65±10.99	11.02±0.62	4.62±0.02	0.89	100.422±1.821
F2	606.8±7.61	11.18±0.85	4.99±0.03	0.91	100.076±1.263
F3	605±6.79	9.44±1.85	4.88±0.05	0.75	101.651±2.123
F4	602±9.47	11.61±0.34	4.76±0.07	0.58	102.93±3.748
F5 std	604.7±12.34	12.19±0.95	4.74±0.10	0.73	104.28±1.902

Table 3. Physicochemical evaluation of all tablet formulation

The main objective of hydroxyzine hydrochloride sustain release tablet is to achive cost effective and effective and efficient sustain release system to deliver at constatant rate .

IV. CONCLUSION AND FUTURE SCOPE:

On the basis of the current study result , it can be concluded that hydroxyzine hydrochloride sustain release tablets were successfully prepared using diffferent polymers by wet granulation techinque . The formulation F1 , F2 , F3 retarted the release of drug up to 07 hours . Formulation F4 controlled the drug release for 10 hours whereas formulation F5 controlled the drug release for 12 hours with the burst effect and through the process of diffusion , and the formulation found to be good due to satesfactory quality attribuites .

REFERENCES:

[1]. Vestergaard C, Toubi E, Maurer M, Triggiani M, Ballmer-Weber B, Marsland A, Ferrer M, Knulst A, Giménez-Arnau A. Treatment of chronic spontaneous urticaria with an inadequate response to H1-antihistamines: an expert opinion. European Journal of Dermatology. 2017 Jan;27(1):10-9.

[2]. Batra N, Acharya A. Sustained Release drug delivery system “Novel Formulation approaches and Drug release profile”. Advances in Multidisciplinary Research and Development. 2022:74.

[3]. Robinson J, Lee VH. Controlled drug delivery: fundamentals and applications. CRC Press; 1987 Jan 30.

[4]. Kuna L, Jakab J, Smolic R, Raguz-Lucic N, Vcev A, Smolic M. Peptic ulcer disease: a brief review of conventional therapy and herbal treatment options. Journal of clinical medicine. 2019 Feb 3;8(2):179.

[5]. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. Philadelphia: Lea &Febiger; 1976.

[6]. Monczor F, Fernandez N. Current knowledge and perspectives on histamine H1 and H2 receptor pharmacology: functional selectivity, receptor crosstalk, and repositioning of classic histaminergic ligands. Molecular pharmacology. 2016 Nov 1;90(5):640-8.

[7]. McKeny PT, Nessel TA, Zito PM. Antifungal antibiotics. InStatPearls [Internet] 2021 May 4. StatPearls Publishing.

[8]. Sah HK, Cho MH, Park S, Yun MO, Kang SJ. Application of SUPAC-MR in Processing Postapproval Changes to Modified Release Sold Oral Dosage Forms. Journal of Pharmaceutical Investigation. 2004;34(3):229-54.

[9]. Hamed R, Omran H. Development of dual–release pellets of the non-steroidal anti–inflammatory drug celecoxib. Journal of Drug Delivery Science and Technology. 2020 Feb 1;55:101419.

[10]. Suslina S, Alkhodri A. Preparation, evaluation and development celecoxib prolonged release (PR) tablets by using cellulose polyacrylic acid-based polymers. Research Journal of Pharmacy and Technology. 2022;15(4):1727-31.

[11]. Gupta E, Barends DM, Yamashita E, Lentz KA, Harmsze AM, Shah VP, Dressman JB, Lipper RA. Review of global regulations concerning biowaivers for immediate release solid oral dosage forms. European journal of pharmaceutical sciences. 2006 Nov 1;29(3-4):315-24.

[12]. Shah VP, Konecny JJ, Everett RL, McCullough B, Noorizadeh AC, Skelly JP. In vitro dissolution profile of water-insoluble drug dosage forms in the presence

of surfactants. Pharmaceutical research. 1989 Jul;6(7):612-8.

[13]. Meyer MC, Straughn AB, Jarvi EJ, Wood GC, Pelsor FR, Shah VP. The bioinequivalence of carbamazepine tablets with a history of clinical failures. Pharmaceutical research. 1992 Dec;9(12):1612-6.

[14]. Drug DP. Guidance for industry. Center for Drug Evaluation and Research (CDER). 1998 Oct;1000.

[15]. Thompson KA, Goodale DB. The Recent Development of Propofol (DIPRIVAN^ sup®^). Intensive care medicine. 2000 Dec 1;26:S400.

[16]. Skelly JP, Van Buskirk GA, Savello DR, Amidon GL, Arbit HM, Dighe S, Fawzi MB, Gonzalez MA, Malick AW, Malinowski H, Nedich R. Scale-up of immediate release oral solid dosage forms. Pharmaceutical research. 1993 Feb 1;10:313-.

[17]. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles. Pharmaceutical technology. 1996;20(6):64-74.