FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLET OF CINNARIZINE AND DIMENHYDRINATE

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Abstract

The main goal is to give immediate action of both the drugs Cinnarizine and Dimenhydrinate which is required in vertigo. All the batches for tablet were prepared by direct compression method in which AVICEL PH 102 was used as direct compressible agent. Simultaneous equation method was done for assay and % drug release characterization. 2^3 factorial experimental design was applied, and three different superdisintegranting agent use as independent variable i.e. sodium starch glycolate, Crosscarmellose sodium and crosspovidone. In batches add these different superdisintegranting agents and concentration use 2, 3 and 5%. The hardness and tablet weight were fixed throughout the experiment i.e. 5kg/cm^2 and 200 mg respectively. From that -1 level for superdisintegrants was selected as 0% and +1 level was selected as 4%. The three superdisintegrants were selected as independent factor and disintegration time was selected as dependent factor. In the trial batches the formula F9 (contain 5% crospovidone) shows the lowest disintegration time (6 seconds) and wetting time (10 seconds). All the test parameters were found to be within specified limit. In the factorial batches the formulation as shows lowest disintegration time (25 seconds) which contains 4% of two superdisintegrants i.e. sodium starch glycolate and crosspovidone whereas the formulation 1 shows highest disintegration time (151 seconds) which contains no superdisintegrants. From that 3 optimize batches (O1-O3) were selected, formulated and evaluated which shows satisfactory result. O1 formulation was selected as best formulation.

Key word:-Immediate release, superdisintegrants, direct compression, disintegration time, wetting time.

Introduction

Many patients find difficulty to swallow tablets and hard gelatine capsules; consequently they do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem which results in a high incidence of incompliance and ineffective therapy. For this reason the development of an orally disintegrating or rapidly disintegrating tablet (RDT) has recently interested not only the pharmaceutical industry [1]. In order to achieve rapid disintegration rate, the tablet formula must provide a high porosity, low density and a low hardness. Over a decade, the demand for development of immediate release tablets (IRTs) has enormously increased, as it has significant impact on the patient compliance. Immediate release tablets offer an advantage for populations who have difficulty in swallowing. Immediate release tablets with good taste and flavor increase the acceptability of bitter drugs by various groups of population. However, of all the above terms, the United States Pharmacopoeia (USP) approved these dosage forms as immediate release tablets or IRTs United States Food and Drug Administration (FDA) defined IRT as ‘‘A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue’’.[2]

Immediate release tablets offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include, as IRTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients; no risk of obstruction of gastrointestinal tract by the dosage form, which is beneficial for traveling patients who do not have access to water, easy administration for pediatric, geriatric, and inpatients (specially for mentally retarded and psychiatric patients); the rapid disintegration of the tablet results a quick dissolution of the drug and fast absorption that provide rapid onset of action; bioavailability of drugs that are absorbed in the mouth, pharynx, and esophagus is increased; and pre-gastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increases the bioavailability of the drug. Patients appreciate the convenience and the discreteness of these products which can be taken without water and which guaranty a rapid onset of action. Commercially available IRT are

prepared by various techniques, mainly lyophilisation, molding and direct compression. The lyophilisation and molding techniques produce IRT which disintegrate within about 30s, but that have low physical resistance and high friability. On the other hand, tablets obtained by direct compression are less friable but disintegrate in a longer time.

The most important properties of these tablets are: mechanical strength, friability, taste, grittiness and the *in vivo* disintegration time. After choosing the manufacturing technique and the appropriate tablet composition, the most important issues are manufacturing circumstances and optimal tablet composition. In addition to the pharmacopoeial requirements, tablets should have an acceptable taste and very short disintegration time in the mouth. In the course of developing a new dosage form, several different compositions and manufacturing parameter combinations are tested. Therefore, it is important to possess in vitro measurements for the determination of each relevant tablet parameter, including the disintegration time [3,14].

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period. Have a pleasing mouth feel. It should not leave minimal or no residue in the mouth after oral administration. Rapid dissolution and absorption of drug, which may produce rapid onset of action. Decreased disintegration and dissolution times for immediate release oral dosage forms. Improved compliance/added convenience. Improved stability, bioavailability. Allows high drug loading. Adaptable and amenable to existing processing and packaging machinery. Cost- effective improved solubility of the pharmaceutical composition.

Cinnarizine is an antihistamine and a calcium channel blocker. Dimenhydrinate acts by antihistamines as well as anti-emetic, anti-motion sickness, and anti-vertigo effects. Both this drugs are use for the treatment of vertigo. Vertigo is an illusion of rotation. It is due to unequal neural activity between the left and right vestibular nuclei.

MATERIAL AND METHOD:-

Material

Cinnarizine was purchases from Balaji drugs, Surat, Dimenhydrinate was gifted by S. S. Pharmachem, Boisar (SAM\DMN\051352), Croscarmellose sodium (FN000240), Crosspovidone (4766352400), Sodium starch glycolate (E2328), Mannitol (201302054), Microcrystalline cellulose PH 102 (0047) were gifted by Sun pharma silvassa, Magnesium stearate (SUN Pharma, Silvassa A/161212), Talc (SUN Pharma, Silvassa X/900-002). All ingredients and solvent analytical grade.

Method and Preparation of Immediate release tablets of drugs:-

Weigh all the ingredients according to formula shown in Table 1. Pass all the ingredients individually through sieve #60. Mix all the ingredients except talc and magnesium stearates in mortar pastel according to geometric dilution. Pass talc and magnesium stearates through sieve #60 and add mixture, mix all this mass for 5minutes. Compress it in 8mm punch on 16 station rotary tablet compression machine (Hardik Engg, Ahmedabad) with hardness 5 kg/cm^2.

Table 1: Composition of immediate release tablet for trial batches

Ingredients									
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cinnarizine	20	20	20	20	20	20	20	20	20
Dimenhydrinate	40	40	40	40	40	40	40	40	40
SSG*	4			6			10		
CCS+		4			6			10	
CP×			4			6			10
Mannitol	50	50	50	50	50	50	50	50	50
Avicel PH 102	81	81	81	79	79	79	75	75	75
Magnesium stearates	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Total wt (mg)	200	200	200	200	200	200	200	200	200

All the values taken in mg
* SSG = Sodium starch glycolate, + CCS = Croscarmellose sodium and × CP = Crospovidone

Evaluation of Immediate release tablet [15, 16]

1. Size & Shape [4]

Tablet thickness was measured by vernier caliper. Tablet thickness should be controlled within a ± 5% variation of standard value.

2. Hardness [4]

Hardness generally measures the tablet crushing strength. It was measured by Monsanto Hardness Taster.

3. Friability [5]

Friability of a tablet was determined by Roche friabilator. This consists of a plastic chamber that revolves at 25 rpm, dropping the tablets through a distance of six inches in the friabilator, which was then operating for 100 revolutions. The tablets are reweighed and % loss calculated using following equation:

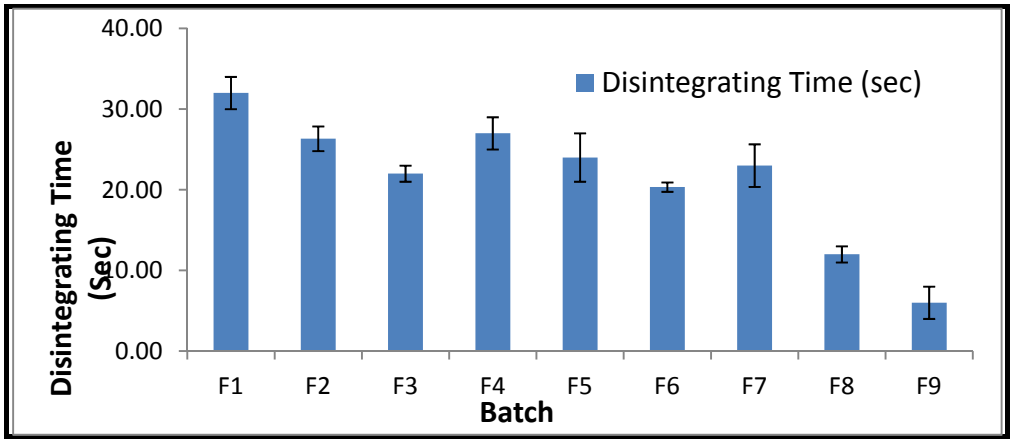
$$\% \, Friability = \frac{Initial\ Weight - Final\ Weight}{Initial\ Weight} \times 100$$

4. Weight variation test [6]

Twenty tablets were selected at random and average weight was determined using an electronic balance. Tablets were weighed individually and compared with average weight.

5. Disintegration test [7]

Disintegration time was measured using a rapid disintegration tablet tester. Purified water was used as medium. The medium temperature was kept at 37°C. Each tablet was placed on the wire gauze, slightly immersed in the medium, and then compressed by the shaft. The compression force was easily adjusted using the weight. The tablet was crushed by the rotary shaft and the tablet disintegrated into the medium. The time was counted between the times that the weight touched the tablet and the wire gauze and reported as disintegration time. The rotation speed and weight were set at 25 rpm and 15 g, respectively. Measurements were repeated three times and the average was reported in figure 1.



6. Wetting time [8]

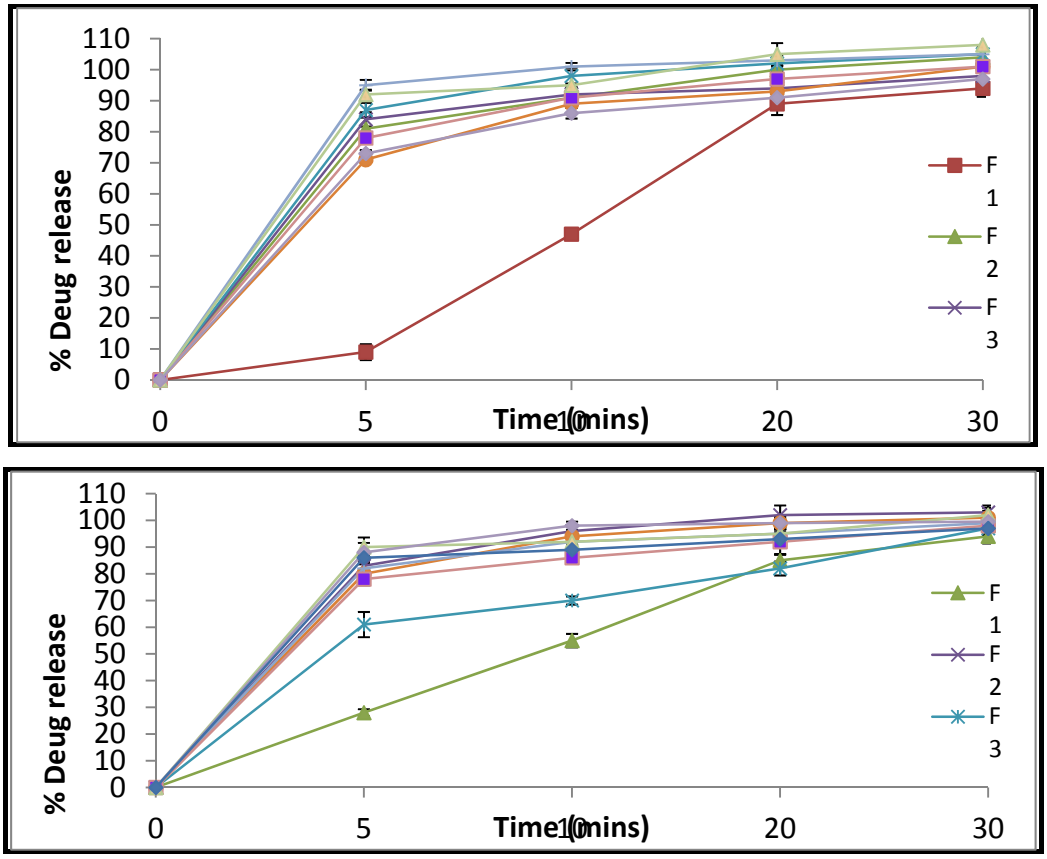
Flat tissue papers of 2×2 cm were placed in a Petri-dish before putting Petri-dish tissue paper wetted with medium pinch of amaranth was place top of tablet. One tablet was carefully placed on the surface of the tissue paper. The time required for develop color due to amaranth water soluble dye on the upper surface of the tablets was noted as the wetting time.

7. Drug Content (Assay) [9]

Crush tablets and add weigh appropriate amount of powder and dissolved in methanol, sonicate for 5 minutes and filtered; and by suitable dilution with 0.1 N HCl pH 1.2 and analysis in UV spectroscopy at λ_{max} Cinnarizine 253.2nm /Dimenhydrinate 276.2nm. Find out the drug content by simultaneous equation method.

8. *In vitro* Dissolution study [10]

Dissolution study was carried out in USP type I apparatus according to with 900 ml. It was carried out in 0.1N HCl pH 1.2 of 900 ml and temperature at 37±5ºC. The samples were withdrawn at 5, 10, 20 and 30 minutes and add adequate passing media sample analysis was in UV spectrophotometer at 251.2 and 276.2 nm was reported in figure 2 and 3.



RESULT AND DISCUSSION

Immediate release tablet is needed to give action immediately; here the two drugs were incorporated i.e. Cinnarizine and Dimenhydrinate which were used as fixed dose combination in the dose of 20 mg and 40 mg respectively. Both the drugs are used in the treatment of vertigo (vertigo need to treated quickly); so the immediate release tablet was advantageous. Clinically when both drug used, dose is reduced. (Normal dose of Cinnarizine and Dimenhydrinate are 3×30 mg/day and 3×50-80 mg/day respectively) but when they are in fixed dose combination their dose are reduced to 20 mg and 40 mg respectively [11, 12, 13]. Both the drugs are the BCS class II but there solubility in 0.1 N HCl pH 1.2 were found to be 355.9 mg/L for Cinnarizine and 84 mg/L for Dimenhydrinate which are acceptable. Both the drugs are well absorbed throughout GIT.

Tablets were prepared by direct compression method. Throughout the work the hardness and tablet weight was fixed to 5 kg/cm^2 and 200 mg respectively. 8mm punch was used to prepare the tablets. AVICEL PH 102 was used as direct compressible agent. Nine trial batches taken as preliminary batches in which the different superdisintegrants were used in different concentration i.e. 2, 3 and 5%. In which5% superdisintegrant when used it shows lowest disintegration time (F9 containing 5% crospovidone shows disintegration time 6 seconds). It was then evaluated for thickness, diameter, friability, weight uniformity test, disintegration time, wetting time, drug content and *in vitro* dissolution study.

The present work was to screaming and optimization of disintegrating agents like Sodium starchglycolate, Crosscarmellose sodium and crosspovidone were used as a factor adds physiochemical parameter and disintegration time was used for screaming and disintegrating agent. Disintegration time of different formulation was found to be 6-32 seconds. And it was observed that when the concentration of superdisintegrants when increased the disintegration time decreased. F9 formulation (containing 5% of CP) shows lowest disintegration time i.e. 6 seconds whereas disintegration time of formulation F3 andF6 shows 22 and 20 seconds respectively containing 2 and 3% of CP. Whereas CCS shows better result as compare to SSG. The disintegration time of F1, F4 and F7formulations were found to be 32, 27 and 25 seconds respectively which contains SSG as superdisintegrant in the concentration of 2, 3 and 5% respectively. Whereas formulation F2, F5 and F8 shows disintegration time of 25, 24 and 21 seconds that contain CCS as superdisintegrant in the concentration of 2, 3 and 5% respectively. So the order of decrease in disintegration time was SSG > CCS > CP containing formulation. Three different superdisintegrants were used i.e. sodium starch glycolate, crosscarmellose sodium and crosspovidone. These different superdisintegrants were responsible to decrease the disintegration time when their concentration increases. Wetting time of different formulation was found to be 10-35 seconds. F9 formulation (containing 5% of CP) shows lowest wetting time i.e. 10 seconds. Whereas CCS shows better result

as compare to SSG. The wetting time of F1, F4 and F7 formulations was found to be 35, 31 and 27 seconds respectively; which contains SSG as superdisintegrant in the concentration of 2, 3 and 5% respectively. Whereas formulation F2, F5 and F8 shows wetting time of 29, 26 and 23 seconds that contain CCS as superdisintegrant in the concentration of 2, 3 and 5% respectively.% drug content for Cinnarizine was found to be 97.84-109.12 which passes the test criteria (90-110%). And % drug content for Dimenhydrinate was found to be 90.83-103.14 which passes the test criteria (90-110%).

Conclusion

This study successfully indicated that appropriate immediate release tablets. Immediate release tablet is needed to give rapid action. Here the two drugs were incoparated i.e cinnarizine and dimenhydrinate which were used as fixed dose combination in the dose of 20 mg and 40 mg respectively. Both the drugs are used in the treatment of vertigo (vertigo need to treated quickly); so the immediate release tablet was advantageous. Clinically when both drug used, dose is reduced; but when they are in fixed dose combination their dose are reduced to 20 mg and 40 mg respectively. Both the drugs are the BCS class II superdisintegratings were used i.e sodium starch glycolate, cosscarmellose sodium and crosspovidone. These different superdisintegrants were responsible to decrease the disintegration time when their concentration increases. Tablets were prepared by direct compression method. Throughout the work the hardness and tablet weight was fixed to 5 kg/cm^2 and 200 mg respectively. 8mm punch was used to prepare the tablets. AVICEL PH 102 was used as direct compressible agent.

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