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Original Article

COMPARATIVE STUDY OF SUPERDISINTEGRANTS USING ANTIEMETIC DRUG AS A MODEL

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Abstract :
In the present investigation comparison of three different superdisintegrants was carried out by formulating orally disintegrating tablets. Promethazine HCl was used as model drug which is an antiemetic drug. Sodium starch glycolate, croscarmellose and crospovidone were selected as superdisintegrants and each one was used in three different concentrations (2%, 3.5% and 5%). The drug-polymer compatibility was ruled out by FTIR studies. A total of nine formulations (PF1-PF9) were made by direct compression. All prepared formulations were evaluated for weight variation, hardness, friability, drug content, disintegration time, wetting time and *in vitro* drug release parameters. The results of the evaluation parameters for all the nine formulations of promethazine HCl were within the standard limits. The *in vitro* drug release for promethazine HCl tablets of all the formulations (PF1-PF9) was carried out using phosphate buffer pH 6.8 as dissolution medium. Among all the formulations the tablets formulated with crospovidone (PF7-PF9) have shown 91.43 - 98.43% (maximum) drug release at the end of 10 min than sodium starch glycolate and croscarmellose, hence from the present work, it concluded that among three superdisintegrants crospovidone is the ideal superdisintegrant for formulating oral disintegrating tablets for promethazine HCl.

Keywords : Superdisintegrants, promethazine HCl, sodium starch glycolate, croscarmellose, crospovidone

Introduction :

The tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this problem, scientists have developed innovative drug delivery systems known as Orally Disintegrating Tablets (ODT). These are novel types of tablets that disintegrate/disperse/dissolve in saliva[1].

In order to formulate ODT we need special agents called as superdisintegrants. A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Examples of some superdisintegrants are croscarmellose, crospovidone and sodium starch glycolate.

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Microcrystalline cellulose and low substituted hydroxypropylcellulose were used as disintegrating agents in the range of 8:2 – 9:1 to prepare fast dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Sodium starch gycolate, crospovidone and croscarmellose are some of the popular superdisintegrants. Superdisintegrants can act by 4 mechanisms namely swelling, wicking, repulsive force and deformation[2].

Ideal properties of superdisintegrants

Good Compressibility and Flow Properties

If the powders have 12-16% compressibility, they are said to have good flow powders. Crospovidones are significantly more compressible than other superdisintegrants.

Poor Solubility

The solubility of the major component in a tablet formulation can affect both the rate and the mechanism of tablet disintegration. Water soluble materials tend to dissolve rather than disintegrate, while insoluble materials generally produce rapidly disintegrating tablets.

Poor Gel Formation Capacity

Gels can delay dissolution as the drug must first diffuse through the gel layer before being released into the body. Sodium starch glycolate is used as superdisintegrant in tablet formulation at a concentration of 4-6%.

Good Hydration Capacity

Drugs or other excipients, which are hydrophobic and could be adsorbed on disintegrant surfaces, advertently influence the extent of hydration and the effectiveness of these disintegrants. Addition of fast disintegrants of high hydration capacity is reported to minimize this problem, and therefore, enhance dissolution[3].

Complexation

Anionic disintegrants like croscarmellose sodium and sodium starch glycolate may complex with cationic drug actives and slow dissolution. Crospovidone a non-ionic polymer does not interact with cationic drug actives to retard drug release. The effects of superdisintegrants like croscarmellose sodium, sodium starch glycolate and polyplasdone XL on the dissolution behavior of several cationic drugs with varying water solubility reports that polyplasdone XL had a more rapid dissolution rate for the model cationic drugs, irrespective of their aqueous solubilities[4].

Materials and Methods

Promethazine HCl was obtained as gift sample from Mayer Healthcare Pharmaceuticals, Bangalore. Microcrystalline cellulose was obtained from SD fine chemicals. Sodium starch glycolate, croscarmellose and crospovidone were obtained from Shreeji chemicals, Mumbai. Talc, magnesium stearate was obtained from SD fine chemicals. Aspartame, raspberry flavor were obtained from SD fine chemicals.

Methods

In the present investigation direct compression method was employed for the formulation of orally disintegrating tablets of promethazine HCl with three different superdisintegrants in different concentrations (2%, 3.5% & 5%) for their comparative study. promethazine HCl tablets are available in 25 mg and 50 mg doses in the market. Dose of 25 mg is selected for the present study. Microcrystalline cellulose was used as diluent, talc was used as glidant, magnesium stearate as lubricant, aspartame was used as sweetening agent and raspberry flavor was added to improve taste of tablets. The drug and the excipients were passed through #60-sieve. Weighed amount of drug and excipients except magnesium stearate were mixed in a mortar-pestle by geometric addition method for 20 min. The blend was then lubricated by further mixing with magnesium stearate. The mixture blend was subjected for drying to remove the moisture content at 40 to 45 ºC, the mixture was blended with flavor and the powder blend was then compressed on 10 station rotary punching machine (Rimek RSB-4) using 8 mm round shaped punches. A total of nine formulations were prepared by direct compression method, which is shown in Table 1. The tablets of all the nine formulations were subjected for evaluation.

Evaluation of tablets

Thickness: The thickness of tablets was determined by using digital caliper (Coolant proof IP 65). The tablet is placed in between the two jaws of caliper scale and the reading was noted down. Three trials for each formulation were carried out[5].

Hardness: The tablet hardness, which is the force required to break a tablet was measured by using Pfizer hardness tester (S 14). Tablet is squeezed by two jaws. The first machines continually applied force with a spring and screw thread until the tablet started to break. When the tablet fractured, the hardness was read with a sliding scale. Three trials for each formulation were performed. The limit of hardness is 3-6 kg/cm^2.

Friability: Friability is the loss of weight of tablet in container/package due to removal of fine particles from

Keywords : Superdisintegrants, promethazine HCl, sodium starch glycolate, croscarmellose, crospovidone - D S Sandeep

surface. This test is performed to ensure the ability of tablets to withstand shocks during processing, handling, transportation and shipment. The friability of tablets was determined using Roche friabilator (EF-2 USP). Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again. The percentage friability of tablets was calculated using the following formula. The standard limit of friability is not more than 1 %[6].

$$\% \text{ Friability } \frac{\text{initial weight - final weight}}{\text{initial weight}} \text{ X } 100$$

Weight variation: Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The percentage deviation can be calculated using following formula.

$$\% \text{ deviation } \frac{\text{individual weight - average weight}}{\text{Average weight}} \text{ X } 100$$

Drug content: The drug content was estimated to know the percentage of drug present in the tablet. Twenty tablets were weighed and powdered. An amount of powder equivalent to 150 mg of promethazine HCl was dissolved in 100 ml of pH 6.8 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 249.60 nm using UV-Visible spectrophotometer (Shimadzu UV-1700)[7].

In vitro dispersion time: This test was performed for the ability of tablets to breakdown into small fragments in fluid. *In vitro* dispersion time was carried out by dropping a tablet in a Petri dish containing 10 ml of saliva fluid (pH 6.8). The time required for the tablet to disintegrate completely in the fluid was noted down. Three trials for each formulation were carried out[8].

Wetting time: Wetting time of tablet is related to contact angle. Wetting time is another important parameter, which needs to be assessed to give an insight into the disintegration properties of tablets. Lower wetting time implies quicker disintegration of tablets. Wetting time of tablet can be carried out using a piece of tissue paper folded twice was placed in a small Petri dish (ID=6.5cm) containing 6 ml of simulated saliva pH 6.8, a tablet was put on the paper, and the time for complete wetting was measured which gives wetting time of tablet. Three trials for each formulation were performed[8].

In vitro drug release: *In vitro* drug release of the samples was carried out using USP – type II dissolution apparatus (TDT 08L paddle type). The dissolution medium, 900 ml of phosphate buffer (pH 6.8) solution, was placed into the dissolution flask maintaining the temperature of 37±0.5 ºC at 50 rpm. One tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 10 min. Samples measuring 5 ml were withdrawn at an interval of 2, 4, 6, 8 and 10 min. Samples were filtered through 10 µm filter. Same volume of the fresh dissolution medium was replaced every time. The collected samples were suitable diluted and analyzed at 249.60 nm by UV-Visible spectrophotometer (Shimadzu UV-1700) using dissolution medium as blank. The cumulative percentage drug release was calculated[9].

Results and Discussion :

The results of evaluation parameters for the nine formulations are shown in Table 2 & 3. The results of *in vitro* drug release of tablets for all the nine formulations are shown in Table 4, 5 and 6.

The thickness of the tablet indicates that die fill was uniform. The thickness depends upon the size of the punch (8 mm) and the weight of the tablet (150 mg). The thickness of tablets from batch PF1-PF9 was found to be 2.50 - 2.86 mm and hardness was found to be 3.1 - 4.2 kg/cm^2. The friability of all the formulated tablets of promethazine HCl was found to be between 0.45 - 0.72 % and all the formulated tablets of promethazine HCl were shown the friability within the official limits. The weight variation for the tablets of all the (PF1-PF9) formulations was within the standard limits (±7.5%). All the formulated tablets (PF1-PF9) have shown *in vitro* dispersion time of less than 60 sec.

Among all the formulations, tablets prepared with crospovidone were shown less than 40 sec of dispersion time. The wetting time of all the formulations (PF1-PF9) are found to be within 39.30-68.33 sec which complies with the official limits. The drug content of all the nine formulations of promethazine HCl tablets was found to be within the range of 96.78-99.71% which was within the limits of IP specifications. The formulations PF1-PF3 were formulated with the help of sodium starch glycolate in concentration 2%, 3.5% and 5% respectively. The formulations PF4-PF6 were formulated with the help of croscarmellose in concentration 2%, 3.5% and 5% and the formulations PF7-PF9 were formulated with the help of crospovidone in concentrations 2%, 3.5% and 5% respectively. The formulations PF7-PF9 containing crospovidone shown 91.43-98.43% drug release which was the highest drug release compared to all the other formulations. The drug release profile for all the nine formulations are shown in Figure 1, 2 and 3.

Table 1: Formulation design of promethazine HCl orally disintegrating tablets

Ingredients(mg)	Pf1	Pf2	Pf3	Pf4	Pf5	Pf6	Pf7	Pf8	PF9
Promethazine HCl	25	25	25	25	25	25	25	25	25
SSG	3	5.25	7.5	-	-	-	-	-	-
Croscarmellose	-	-	-	3	5.25	7.5	-	-	-
Crospovidone	-	-	-	-	-	-	3	5.25	7.5
Aspartame	5	5	5	5	5	5	5	5	5
Raspberry flavour	3	3	3	3	3	3	3	3	3
Talc	10	10	10	10	10	10	10	10	10
Magnesium state	3	3	3	3	3	3	3	3	3
MCC(q.s)	150	150	150	150	150	150	150	150	150

Table 2 : Results of thickness, hardness, friability and weight variation of promethazine HCl tablets

Formulation code	*Thickness (mm)	*Hardness (kg/cm^2)	Friability (%)	Weight variation
Pf1	2.62±0.01	3.7±0.38	0.51	149.10±0.20
PF2	2.63±0.07	3.4±0.33	0.48	151.09±0.33
PF3	2.66±0.02	3.4±0.65	0.45	150.19±0.21
PF4	2.63±0.05	4.2±0.25	0.72	150.33±1.76
PF5	2.52±0.01	3.8±0.31	0.70	148.80±1.03
PF6	2.53±0.05	3.8±0.72	0.67	150.33±2.12
PF7	2.51±0.05	3.2±0.22	0.64	149.60±1.28
PF8	2.50 ±0.05	3.1±0.30	0.60	150.43±1.71
Pf9	2.65 ±0.03	3.8±0.38	0.54	151.67±1.27

*Value expressed as mean ±SD, n=3

Table 3 : Results of *in vitro* dispersion time, wetting time and water absorption ratio of promethazine HCl tablets

Formulation code	**In vitro* dispersion time (sec)	*Wetting time (sec)	% Drug content
PF1	58.00±4.13	68.33±3.51	98.21±0.66
PF2	55.33±4.16	64.13±3.81	98.21±0.66
PF3	40.33±3.18	48.12±3.21	96.78±0.86
PF4	54.21±3.10	60.65±3.00	98.55±0.76
PF5	48.11±4.10	54.00±4.00	98.73±1.10
PF6	45.33±3.11	50.33±3.11	98.22±0.38
PF7	38.00±1.98	50.21±3.05	99.28±0.28
PF8	27.66±2.51	44.00±2.31	98.91±0.81
PF9	18.34±1.15	39.30±1.54	99.71±0.16

*Value expressed as mean ±SD, n=3

Table 4 : *In vitro* drug release data of promethazine HCl tablets formulated with sodium starch glycolate

SR. No.	Time (min)	% Cumulative drug release		
		Pf1	Pf2	PF3
1	0	0	0	0
2	2	31.23±0.65	35.87±0.21	38.67±0.96
3	4	37.98±1.12	42.87±1.12	43.12±0.54
4	6	46.80±1.23	48.40±0.76	57.54±0.43
5	8	52.54±0.76	56.65±0.76	65.78±0.54
6	10	58.85±0.98	63.87±0.75	72.78±1.10

Table 5 : *In vitro* drug release data of promethazine HCl tablets formulated with croscarmellose

SR. No.	Time (min)	% Cumulative drug release		
		Pf4	Pf5	PF6
1	0	0	0	0
2	2	32.67±0.23	36.19±0.34	35.28±0.87
3	4	43.12±0.67	44.78±1.45	47.32±1.15
4	6	57.54±0.65	59.63±1.00	60.22±0.37
5	8	65.78±0.78	68.20±1.32	73.73±0.62
6	10	72.78±1.15	74.87±0.78	82.65±0.47

Table 6 : *In vitro* drug release data of promethazine HCl tablets formulated with crospovidone

SR. No.	Time (min)	% Cumulative drug release		
		Pf7	Pf8	PF8
1	0	0	0	0
2	2	42.76±0.76	45.72±0.73	47.98±1.00
3	4	55.87±0.43	59.98±0.54	62.12±0.62
4	6	72.50±1.32	75.65±0.32	79.43±0.91
5	8	84.92±1.12	89.64±0.65	88.90±0.47
6	10	91.43±0.63	94.34±1.34	98.43±1.27

Keywords : Superdisintegrants, promethazine HCl, sodium starch glycolate, croscarmellose, crospovidone - D S Sandeep

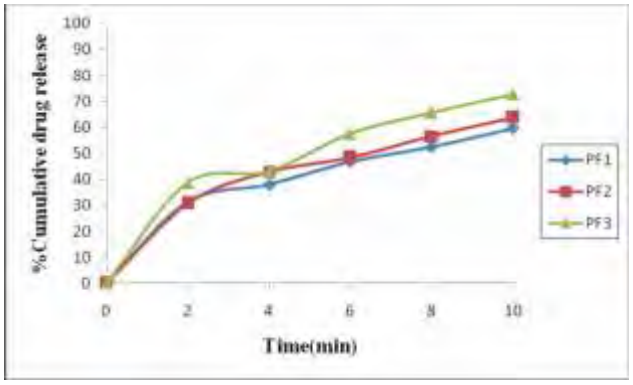

Figure 1: *In vitro* drug release profile of promethazine HCl tablets formulated with sodium starch glycolate

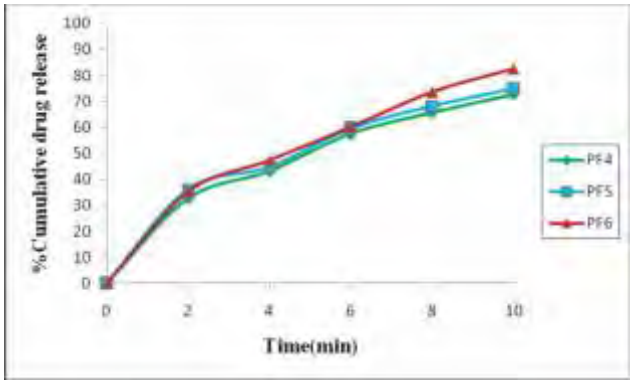

Figure 2 : *In vitro* drug release profile of promethazine HCl tablets formulated with crosscaremelose

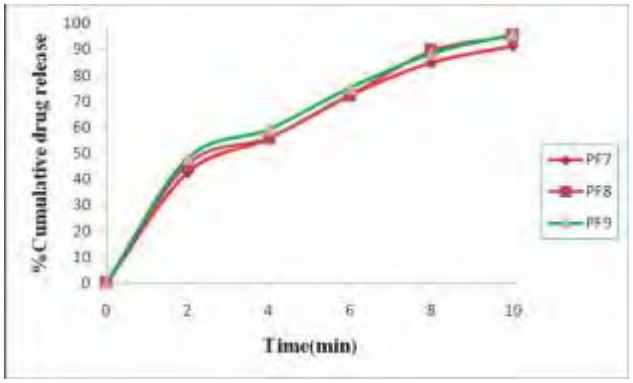

Figure 3 : *In vitro* drug release profile of promethazine HCl tablets formulated with crospovidone

Conclusion :

A comparative study of three superdisintegrants (sodium starch glycolate, croscarmellose and crospovidone) was carried out using promethazine HCl as model drug by formulating nine batches (PF1-PF9) by direct compression method. The tablets were evaluated for parameters like thickness, hardness, friability, *in vitro* dispersion time, wetting time and percentage drug content. All the evaluation parameters of nine formulations were found to be within the IP limits. All the formulated tablets were examined for *in vitro* drug release studies. Among the three superdisintegrants, crospovidone showed maximum percentage drug release and hence it was found to be the ideal superdisintegrant for the formulation of promethazine HCl orally disingrating tablets.

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