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Formulation and *in-vitro* evaluation of levocetirizine dihydrochloride orodispersible tablets

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ABSTRACT

Orodispersible tablets, also called as mouth dissolving tablets, are the formulations which dissolve or disperse in the saliva and do not require water for administration, thus are good alternative for travelers, bed ridden patients, dysphagic, geriatric and pediatric patients. The purpose of the present study was to formulate orodispersible tablets of levocetirizine dihydrochloride as it quickly disintegrate and disperse in the saliva. Superdisintegrants like Sodium starch glycolate (SSG), Crosscarmellose sodium (CCS) and Crosspovidone(CP) were used for the formulation. A total of twelve batches were formulated. The tablets were fabricated by direct compression method. All the formulations were subjected to in-vitro tests like wetting time, disintegration test and dissolution test. The effect of superdisintegrants on wetting time, disintegration time and dissolution profile was evaluated. The in-vitro study showed that increasing the concentration of superdisintegrants lowers the wetting time (WT) and disintegration time (DT) and enhances the drug release percentage of the formulations. The formulation with SSG 6% and CP 4.5% was the most effective formulation as it showed wetting time of 25 seconds, disintegration time of 30 seconds and cumulative % drug release of 68.12 and 104.20% at 1 and 10 minutes respectively. The study showed that the formulations containing SSG and CP as the superdisintegrants showed better drug release pattern than the formulations with other superdisintegrants. The study also showed that SSG as the superdisintegrant was more effective for the formulation of orodispersible tablets of levocetirizine dihydrochloride.

Keywords: Disintegration time, Drug release, Levocetirizine dihydrochloride, Superdisintegrants, Orodispersible tablets.

INTRODUCTION

Mouth dissolving drug delivery systems (MDDDS) are a new generation of drug delivery system which combines the advantages of both liquid and conventional tablet formulations. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. MDDDS offer the luxury of much more accurate dosing than the primary alternative, oral liquids. Mouth-dissolving tablets are also called as fast dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. However, of all the above terms United States Pharmacopoeia (USP) approved these dosage forms as orally disintegrating tablets (ODTs). United States Food and Drug Administration (FDA) defined ODTs as “A solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue”. According to European pharmacopoeia, these MDTs should dissolve/disintegrate in less than three minutes [1].

Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. As they dissolve/disintegrate very fast when placed in the mouth, MDDDS are the most convenient dosage forms for dysphasic, pediatric and geriatric patients with swallowing problem. They do not

require water for administration, thus are good alternative for travelers and for bed ridden patients. They simply vanish when placed in the mouth, so cannot be hidden in mouth by psychotic patients. These products not only increase the patient's compliance but also fetch large revenues to manufacturers due to line extension of the existing formulation. In the recent past, several new advanced technologies have been introduced for the formulation of mouth dissolving tablets (MDTs) with very interesting features, like extremely low disintegration time, exceptional taste masking ability, pleasant mouth feel and sugar free tablets for diabetic patients. The technologies utilized for fabrication of MDDDS include direct compression lyophilization, moulding, cotton candy process, spray drying, sublimation, mass extrusion, nanonization and quick dissolve film formation. These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets. The formulations prepared from these techniques differ from each other on the basis of the factors like mechanical strength of final product, drug and dosage form stability, mouth feel, taste, rate of dissolution of the formulation in saliva, rate of absorption from saliva and overall drug bioavailability [2]. Among the before mentioned methods easiest way to manufacture orodispersible tablets is direct compression. Low manufacturing cost, conventional equipments and limited number of processing steps lead this technique to be a preferable one [3].

The basic approach used in development of MDT is the use of superdisintegrants like Crosslinked carboxymelhylcellulose (Croscarmeliose), Sodium starch glycolate (Primogel, Explotab). Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva [4].

Levocetirizine is a third-generation non-sedative antihistamine, developed from the second-generation antihistamine cetirizine. Chemically, levocetirizine is the active enantiomer of cetirizine. It is the L-enantiomer cetirizine racemate. Levocetirizine works by blocking histamine receptors. It does not prevent the actual release of histamine from mast cells, but prevents it binding to its receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area, and provides relief from the typical symptoms of hay fever.

In general levocetirizine has low oral bioavilability because of high first pass metabolism rate [5] thus formulation in orodispersible form of levocetirizine enhances the bioavailability, decreases side effects, low dosing, patient compliance, rapid onset of action with good stability.

In the current work, orodispersible tablets of levocetirizine dihydrochloride were prepared by direct compression method using Croscarmellose sodium, sodium starch glycollate and crospovidone as the superdisintegrants. The aim of the study was to evaluate the effect of the superdisintegrants on wetting time, disintegration time and drug release profile of the orodispersible tablets.

EXPERIMENTAL SECTION

Materials

Levocetirizine dihydrochloride was used as the active ingredient. Croscarmellose sodium, sodium starch glycolate and crosspovidone were used as the superdisintegrants. The other ingredients used were mannitol, aerosol, magnesium sterate, aspartame, mint flavor and microcrystalline cellulose PH 102. The active drug was obtained as a gift sample from SR Drug Laboratories Pvt. Ltd, Kathamndu. Crospovidone was received as gift sample from Lomus Pharmaceuticals Pvt. Ltd, Kathmandu. The other excipients and chemicals used in experimental works were obtained from Nova Genetica pharmaceuticals Pvt. Ltd, Dhading, Nepal. All reagents used were of analytical grade.

Methods

Preparation of orodispersible tablets of levocetirizine dihydrochloride

The composition of different formulation of levocetirizine dihydrochloride orodispersible tablets is shown in Table 1. Levoretirizine dihydrochloride and all other excipients were weighed separately and passed through sieve number 60. The active drug was mixed with MCC PH102. Then the remaining excipients except the lubricants were blended with the active drug- MCC blend. The lubricants were then blended to the mix to form the final blend. The final blend was then compressed on 10 station rotary compression machine using 8 mm punch.

In-vitro wetting time studies

Circular tissue papers of 10cm diameter were placed in a petridish containing 10 ml of buffer solution simulating saliva, pH 6.8, and amaranth. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was recorded [6].

Table 1: Formulation composition of levocetirizine dihydrochloride orodispersible tablets

S. No.	Ingredients (mg/tablet)	BS1	BS2	BS3	BS4	BS5	BS6	BS7	BS8	BS9	BS10	BS11	BS12
1.	Levocetirizine dihydrochlorde	5	5	5	5	5	5	5	5	5	5	5	5
2.	Sodiumstarchglycolate	12	12	3	3	12	12	3	3	-	-	-	-
3.	Crosspovidone	9	3	9	3	-	-	-	-	9	9	3	3
4.	Croscarmellose Sodium	-	-	-	-	6	3	6	3	6	3	6	3
5.	Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
6.	Aerosol	2	2	2	2	2	2	2	2	2	2	2	2
7.	Magnesium state	1	1	1	1	1	1	1	1	1	1	1	1
8.	Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
9.	Flavor(mint)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
10.	Microcrystalline cellulose	137	143	146	152	140	143	149	152	143	146	149	152
	Total	200	200	200	200	200	200	200	200	200	200	200	200

In- vitro disintegration studies

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. Water was used at the media for the study. The water was maintained at a temperature of 37°±0.5°C and time taken for the entire tablet to disintegrate completely was noted.

In- vitro dissolution studies

In vitro dissolution studies for all the fabricated tablets was carried out by using USP Type II apparatus (USP XXIII Dissolution Test Apparatus) at 50 rpm in 900 ml of phosphate buffer pH 6.8, maintained at 37±0.5ºC. 5 ml aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and assayed spectrophotometrically at 231nm using dissolution medium as blank. An equal volume of fresh medium, which was pre warmed at 37^0C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Dissolution studies were performed in triplicate. Then the cumulative percentage of drug release was calculated using the following formula.

$$= \frac{\text{spl abs}}{\text{std abs}} \times \frac{\text{std wt}}{\text{spl wt}} \times \frac{\text{spl dil}}{\text{std dil}} \times \frac{\text{std potencys}}{100} \times \text{conversion factor} \times 100\ \%$$

RESULTS AND DISCUSSION

In- vitro wetting time and disintegration time

The result of the wetting time and disintegration test has been shown in table 2

Table 2: In-vitro wetting time and disintegration time of levocetirizine dihydrochloride orodispersible tablets

S.N.	Batch No.	Wetting Time (sec)	Disintegration time (sec)
1	BS1	25	30
2	BS2	31	35
3	BS3	36	40
4	BS4	41	48
5	BS5	25	28
6	BS6	32	34
7	BS7	43	49
8	BS8	44	50
9	BS9	40	44
10	BS10	41	46
11	BS11	42	48
12	BS12	48	54

Effect of **Sodium starch glycolate and Crospovidone**

Batches BS1, BS2, BS3 and BS4 were formulated using Sodium starch glycolate and Crospovidone as the superdisintegrants. The comparison of their disintegration time and wetting time profile is given in figure 1.

Among the different concentrations of superdisintegrants sodium starch glycolate and Crospovidone in the above given formulations, the most effective formulation is BS1 as it has disintegration time of 30 second and wetting time is 25 seconds. While BS2 , BS3 and BS4 have disintegration time of 35 secs, 40 secs, 48 secs respectively and wetting time of 31 secs, 36 secs, and 41 secs respectively. Increasing the concentration of sodium starch glycolate and crospovidone decreases the disintegration time. Sodium starch glycolate can be used from 2% upto 8%, optimum concentration is 4% [7]. Increasing concentration of Crospovidone containing tablets rapidly exhibits high

capillary activity and pronounced hydration with a little tendency to gel formation and disintegration the tablets rapidly [8].

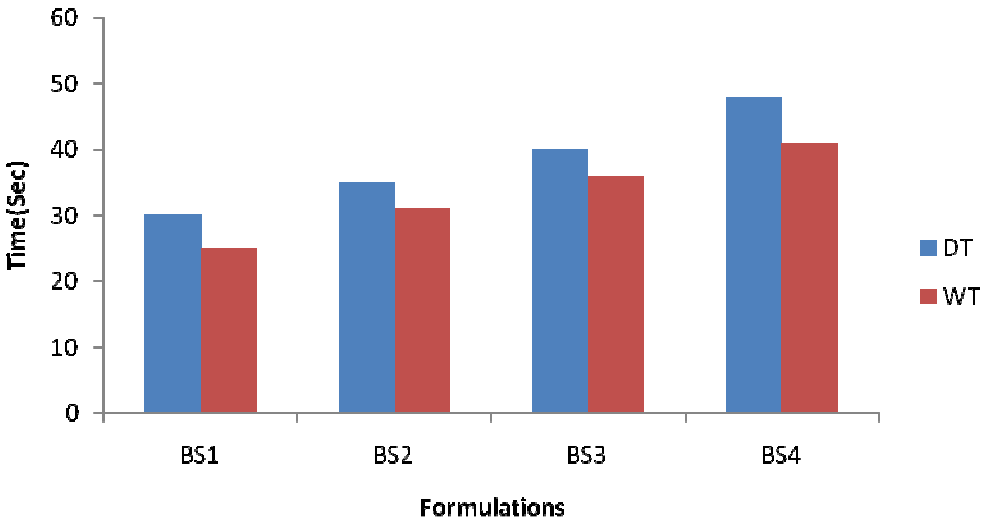

Figure 1: Disintegration time and wetting time comparison between various concentration of sodium starch glycolate and Crospovidone

A study on the formulation of levocetirizine dihydrochloride orodispersible tablets carried out by Gandhi, SG et al., using direct compression method found that increasing the concentration of Crospovidone showed the faster disintegration of the tablet with time 12 second [9].

Effect of Sodium starch glycolate and Croscarmellose sodium

Formulation BS5, BS6, BS7 and BS8 were fabricated using Sodium starch glycolate and Croscarmellose sodium as the superdisintegrants. The comparison of their disintegration time and wetting time profile is given in figure 2.

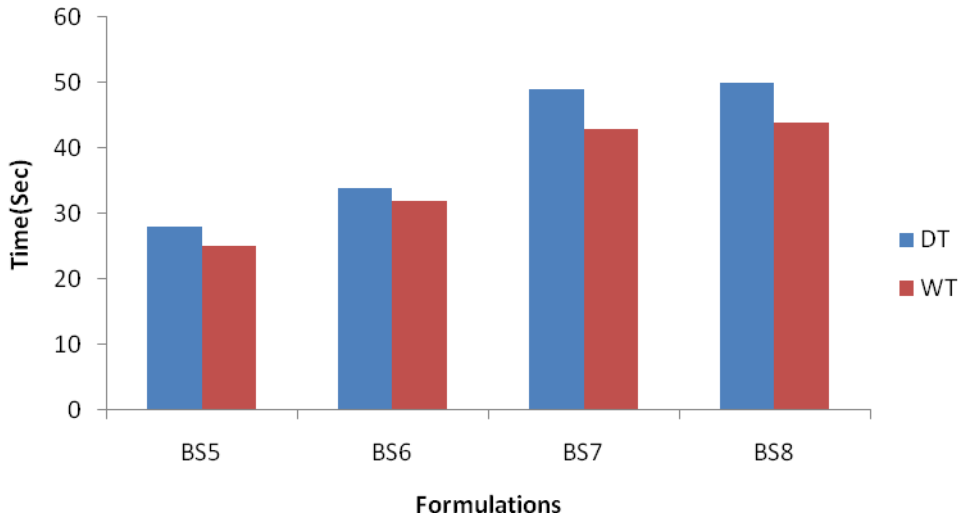

Figure 2: Disintegration time and wetting time comparison between various concentration of sodium starch glycolate and Croscarmellose sodium

Among the different concentrations of superdisintegrants sodium starch glycolate and Croscarmellose sodium in the above given formulations, the most effective formulation is BS5 as it has the disintegration time of 28 second and wetting time is 25 second. While BS6 , BS7 and BS8 have disintegration time of 34 sec, 49 sec, 50 sec respectively and wetting time of 32 sec, 43sec, 44 sec respectively. Increasing the concentration of sodium starch glycolate and croscarmellose sodium decreases the disintegration time. Sodium starch glycolate can be used from 2% to 8%, optimum concentration is 4%. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression [7].

In a study carried out for formulation development and evaluation of mouth dissolving tablets of levocetirizine dihydrochloride by direct compression method using Sodium starch glycolate and Croscarmellose, the result showed that the formulation containing higher concentration of CCS and SSG had the DT of 29 secs [10]. This finding is in consistent with the finding of the present study.

Effect of Crospovidone and Croscarmellose Sodium

Formulation BS9, BS10, BS11 and BS12 contained Crospovidone and Croscarmellose sodium as the superdisintegrants. The comparison of their disintegration time and wetting time profile is given in figure 3.

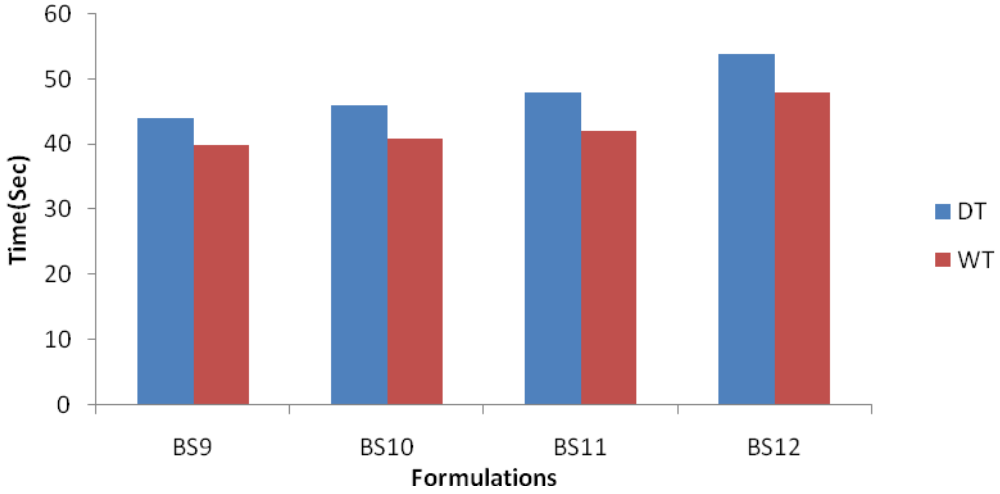

Figure 3: Disintegration time and wetting time comparison between various concentration of Crospovidone and Croscarmellose sodium

Among the different concentrations of superdisintegrants Crospovidone and Croscarmellose sodium in the above given formulations, the most effective formulation is BS9 as it have disintegration time of 44 secs and wetting time is 40 secs. While BS10 , BS11 and BS12 have disintegration time of 46sec, 48 sec, 54 sec respectively and wetting time of 41 secs, 42secs, 48 secs respectively.

The overall result shows that decreasing the concentration of superdisintegrants increases the wetting time and disintegration time of the orodispersible tablets. The formulation with combination of superdisintegrants like SSG & CP and SSG & CCS gave lower wetting time and disintegration time as compared to the formulation containing the combination of CP & CCS. The finding of the current study is supported by the study carried out by Modi A et al which showed that the formulations prepared by using combination of crosspovidone and sodium starch glycolate as a superdisintigrant showed excellent disintegration time[11]. Crospovidone disintegrate the tablets by wicking mechanism and sodium starch glycolate disintegrate the tablets by swelling mechanism. Both wicking and Swelling action of the combined superdisintegrant provide faster disintegration [12]. Crosspovidone showed better disintegrant activity as compared to Croscarmellose sodium. This might be due to that Crospovidone uses a combination of swelling, wicking and deformation mechanism for rapid disintegration of tablets [13]. The study also shows that the effect of the superdisintegrant on the disintegration time of the orodispersible tablets decreases in the order SSG> CP> CCS. This finding is in consistent with the study carried out by Abu Afzal Mohammad Shakar et al [14]. The faster disintegration of crospovidone tablets may be attributed to its rapid capillary activity and pronounced hydration with little tendency to gel formation as compared to the action of Croscarmellose Sodium [15].

Combination of superdisintegrants and their effects on % of Drug release:

The result of in- vitro dissolution study has been listed in Table 3

Table 3: Dissolution profiles of orodispersible tablets (n=3) of levocetirizine dihydrochloride

S.N.	Time (min)	Cumulative % drug release											
		BS1	BS2	BS3	BS4	BS5	BS6	BS7	BS8	BS9	BS10	BS11	BS12
1	1	68.12	65.00	62.13	55.02	65.45	62.13	60.12	52.01	70.12	67.32	63.84	51.24
2	2	80.14	75.12	74.12	70.12	81.23	78.44	75.24	65.32	75.29	73.36	70.12	60.23
3	3	90.52	86.20	80.34	75.32	89.32	85.23	80.98	70.32	88.66	82.34	78.37	68.31
4	5	99.13	93.24	90.12	86.12	98.12	95.12	88.28	89.29	98.33	96.72	89.12	85.23
5	10	104.20	100.12	97.14	92.12	101.99	100.20	95.12	96.23	102.01	100.10	98.13	95.65

Sodium starch glycolate and Crospovidone

The effect of the combination of SSG and CP on the cumulative % of drug release is given in figure 4.

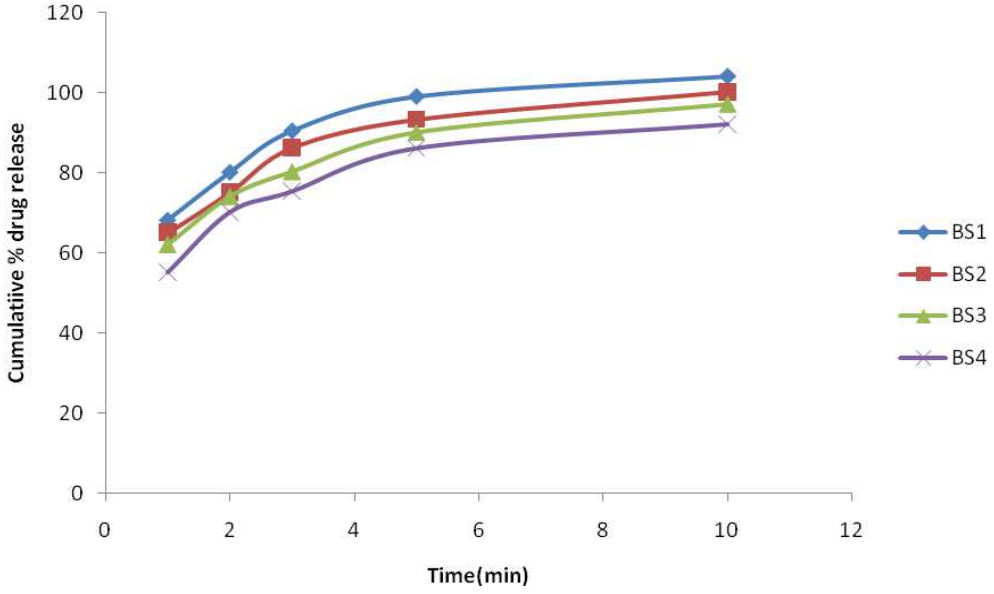

Figure 4: Effect on cumulative % drug release using combination of Sodium Starch Glycolate and Crospovidone

The result shows that increasing the concentration of the superdisintegrantws enhances the drug release percentage. BS2 containing SSG(6%) and CP(1.5%) showed 75.11% drug release and BS3 containing SSG(1.5%) and CP(4.5%) showed 74.12% drug release at 2 minutes. At 10 minutes, BS2 and BS3 showed 100.12 and 97.14% drug release respectively. Overall, the formulations BS2 and BS3 have similar drug release profile. Decreasing the concentration of SSG and CP to 1.5 % (Batch BS4) showed 55.02 % and 92.12% drug release at 1 and 10 minutes respectively. The higher % drug release of formulation BS1 was due to higher concentration of the superdisintegrants.

Sodium starch glycolate and Croscarmellose sodium:

The effect of the combination of SSG and CCS on the cumulative % of drug release is given in figure 5.

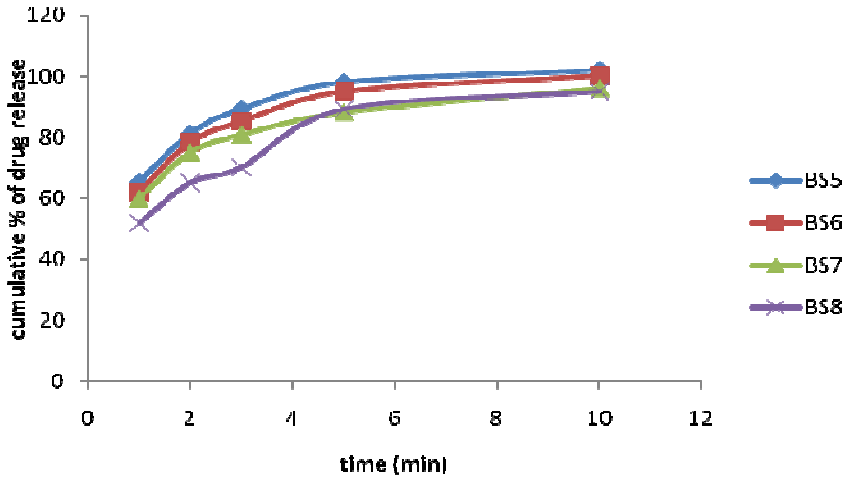

Figure 5: Effect on cumulative % of drug release using combination of Sodium Starch Glycolate and Croscarmellose sodium

Batch BS5 containing SSG(6%) and CP(3%) showed 65.46% and 101.99% drug release at 1 and 10 minutes respectively. Decreasing the concentration of CP to 1.5% decreased the cumulative % drug release to 100.20% at 10 minutes. The result shows that changing the concentration of CP from 3 to 1.5% doesn't show significant difference in drug release profile. Formulation BS8 containing SSG(1.5%) and CP(1.5%) showed 52.01 and 96.23% drug release at 1 and 10 minutes respectively. The current study shows that decreasing the concentration of SSG from 6

to 1.5% significantly decreases the drug release pattern. However at higher concentration of SSG, increasing the concentration of CP from 1.5 to 3% doesn't show significant difference in drug release pattern.

The result shows that SSG, as a superdisintegrant, enhances the drug release pattern as compared to CP. This finding is in consistent with the study carried out by Thakur et al which showed that the formulations containing SSG showed better release of niacinamide as compared to the formulations containing CP and CCS [16]. This is because SSG absorbs water rapidly, resulting in swelling which leads to rapid disintegration of tablets and granules and faster dissolution [17].

Crospovidone and Croscarmellose Sodium:

The effect of the combination of CP and CCS on the cumulative % of drug release is given in figure 6.

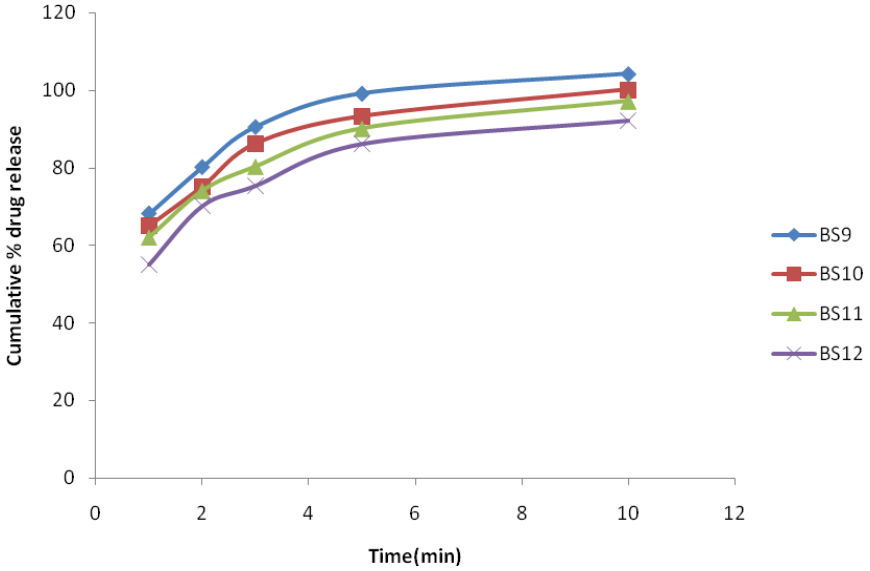

Figure 6: Effect on cumulative % of drug release using combination of Crospovidone and Croscarmellose sodium

Formulation BS9 containing CP(4.5%) and CCS(3%) showed 70.12% and 102.01% drug release at 1 and 10 minutes respectively. Decreasing the concentration of CCS to 1.5% (Batch BS10) decreased the cumulative % drug release to 67.32% and 100.10% at 1 and 10 minutes respectively. Further decreasing the concentration of CP to 1.5% (Batch BS11) rapidly decreased the drug release rate. The in-vitro dissolution study shows that at higher concentration of CP, increasing the concentration of CCS from 1.5 to 3% doesn't show significant difference in drug release pattern. The result also shows that CP is more effective in enhancing the drug release rate as compared to CCS. This is because Crospovidone quickly wicks the dissolution into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration followed by higher rate of drug dissolution [17].

The overall result of the in-vitro dissolution study shows that decreasing the concentration of superdisintegrants lowers the cumulative % drug release of the formulations. The combination of superdisintegrants like SSG and CP shows better drug release profile as compared to other combinations due to the wicking and swelling action of the combined superdisintegrant provide faster disintegration leading to faster rate of drug dissolution [12].

CONCLUSION

The orodispersible tablets of levocetirizine dihydrochloride were prepared by direct compression method. Various combinations of Sodium Starch Glycolate, Croscarmellose sodium and Crospovidone were used as the superdisintegrants for formulating the orodispersible. It was seen that increasing the concentration of the superdisintegrants decreased the wetting time and disintegration time of the formulations. The combination of SSG & CP was more effective in decreasing the disintegration time as compared to the combination of SSG & CCS and CP & CCS. The in-vitro dissolution study showed that the formulation containing SSG (6%) and CP (4.5%) was more effective in enhancing the rate of drug release from the orodispersible tablets. The comparison of the effect of individual superdisintegrant on the wetting time, disintegration time and dissolution showed that SSG was more suitable for the formulation of orodispersible tablets of levocetirizine dihydrochloride as compared to other superdisintegrants used in the current study. Hence from the present study, it can be concluded the superdisintegrant SSG and CP in appropriate concentration can be used to develop orodispersible tablets of levocetirizine dihydrochloride by direct compression method.

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