TASTE MASKING AND FORMULATION OF ONDANSETRON HYDROCHLORIDE MOUTH DISSOLVING TABLETS

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ABSTRACT

This study was done to mask the bitter taste of ondansetron HCl using complexing agent, a polacrilex resin: Tulsion 335 and subsequently forming mouth dissolving tablet using superdisintegrants: Croscarmellose sodium and sodium starch glycollate. A preliminary screening was done. Batch process, a most preferential method for drug loading with ion exchange resins was selected. The process was optimized for drug: resin ratio to get maximum drug loading. A ratio of drug: resin at 1:3 was selected. Taste evaluation was carried out by selecting volunteers. Drug resin complex (DRC) was evaluated for drug release.

The resultant DRC was formulated by direct compression into mouth dissolving tablet using microcrystalline cellulose PH 102, as diluent and croscarmalose sodium and sodium starch glycolate as superdisintegrants and aspartame was used as sweetening agent to enhance palatability. Thirteen formulations were developed by using superdisintegrants: croscarmellose sodium and sodium starch glycolate. Concentration of superdisintegrants ranged from 0.75-9.24 %. The formulated tablet had satisfactory disintegration time and dissolution profile. Optimization was carried out using central composite design. The disintegration and dissolution times were tallied with marketed ondansetron HCl tablets. From the results, it was deduced that the most effective concentration for desired disintegration was of croscarmellose sodium and sodium starch glycollate respectively at concentration above 5%. Therefore, it can be concluded that the intensely bitter taste of ondansetron HCl can be masked by using tulsion 335 and mouth dissolving ondansetron HCl can be successfully prepared by adding aforementioned superdisintegrants. This sort of mouth dissolving ondansetron HCl can be used in controlling vomiting in paediatric and geriatric patients and also for pregnancy induced vomiting.

Key Words: Ondansetron HCl, Complexation, taste masking, ODT, mouth dissolving tablet

INTRODUCTION

Research over the past few years has revealed that ion exchange resins are equally suitable for drug delivery technologies, including controlled release, site-specific fast dissolving, iontophoretically-assisted transdermal, nasal, topical, and taste masked systems [1]. Many research have been conducted on taste masking and formulation of orodispersable Ondansetron HCl. Taste masking were performed by using eudragit EPO, indion 204, ethyl cellulose in different ratios. These were then compressed into tablets by direct compression method with using different superdisintegrants like croscarmellose sodium, crospovidone sodium starch glycolate and glycine-chitosan mixture in different concentrations [2,3,4].

Conventional tablets are intended to be swallowed whole and desired to disintegrate, release the medicaments for dissolution and providing therapeutic efficacy rapidly in the gastrointestinal tract. As disintegration plays a crucial role, so for development of solid orals, formulators are fascinating towards selection of proper disintegrants/ superdisintegrants [3].

Because the disintegration time is related to other formulation variables, a balance has to be maintained between shortening the disintegration time and other tablet properties. FDT formulation that would require fewer excipients than the drug itself would be a breakthrough. The proper choice of a disintegrant or a superdisintegrant and its consistent performance are of critical importance to the formulation development of such tablets. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants. In the formulation superdisintegrants play a key role in determining dissolution of finished drug. Hence type of superdisintegrant, concentration and mode of addition is having greater impact on dissolution profile of drug [4].

The present study is aimed to mask the bitter taste of ondansetron HCl and determine the effect of concentration and mode of addition of superdisintegrants on release.

MATERIALS AND METHODS

Polacrilex resin (Tulsion 335) was the gift sample from CTL Pharmaceuticals, Bhaktapur and Ondansetron HCL was gift sample from Lomus Pharmaceutical Pvt. Ltd, Gothatar VDC, Kathmandu, Nepal. Croscarmellose sodium, sodium starch glycollate, mannitol, MCCPH 102, magnesium stearate, , mix fruit flavour, were received as gift samples from Nova Genetica Pharmaceutical Pvt. Ltd, Naubise VDC, Dhading , Nepal. Other reagents were of analytical grade and were made available in the Kathmandu University laboratory, Dhulikhel.

Preparation of drug resin complex [5]

Five grams of Tulsion 335 (Polacrilex) swollen for 90 minutes in 200 ml of deionized water was added to 5 g of Ondansetron HCl and then stirred for 90 minutes, filtered through Whatmann No. 41. The residue was washed with 100 ml of deionized water and dried.

Optimization of various parameters for maximum drug loading [6, 7]

Drug loading process was optimized for maximum drug loading considering effect of activation, drug: resin ratio and pH as parameters.

Resin Activation

Five g of Tulsion 335, placed on a Whatman filter paper in a funnel, was washed with deionized water and subsequently with 0.1 N HCl (100 ml) or 0.1 N NaOH or combined treatment of 0.1 N HCl and 0.1 N NaOH.

Optimization of drug: resin ratio and pH

Five g of Ondansetron HCl was added to each of the beakers containing 5, 10 and 15 g of resin swelled in 300 ml of deionized water. The mixture was stirred for 90 min. DRC was collected by filtration, washed with 100 ml of deionized water and evaluated for drug content. pH was optimized by preparing DRC using 5 g each of Ondansetron and 15 g resin in 200 ml deionized water and adjusting pH with 1.2, 2, 3, 4, 5, 6, 7, and 8 using standard solutions of hydrochloride and sodium hydroxide. Loading efficiency was determined at these conditions.

Estimation of drug content in DRC

32.53 mg of DRC was stirred with 100 ml of 0.1 N HCl for 60 min so as to release the entire drug from DRC. The mixture was filtered diluted and content determined 310 nm using UV visible spectrophotometer.

In vitro dissolution studies

DRC equivalent to 8 mg of Ondansetron HCl was subjected to USP Type I dissolution at 37±2°C at 50 rpm speed. 500 ml of 0.1 N HCl was used as dissolution medium. DRC equivalent to 8 mg of Ondansetron was placed in basket surrounded by muslin cloth. Aliquot equal to 5 ml was withdrawn after every 2 min. intervals (For total 10 min.) and amount of Ondansetron released from DRC determined at 310 nm [8].

Gustatory Sensation Test

Microparticles containing 8 mg of DRC was dispersed in 25 ml of water for 15 seconds. Then, each volunteer (age 18-22) held about 5 ml of the dispersion in the mouth for 30 seconds. Bitterness level was recorded against pure drug using a numerical scale from 0 to 4 (0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness, and 4: strong bitterness) instantly and then after 30-150 sec. Rinsing the mouth by distilled water and a gap of 30 minutes were applied between successive tests. Based on the opinion of the volunteers, threshold bitterness concentration of DRC was judged *[9]*.

Pre compression parameter studies

The DRCs evaluated for bulk density, tap density, compressibility, angle of repose and flow rate [10]

Development of mouth dissolving tablet

Composition of tablets was:

Ingredients (mg)	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9	A_{10}
DRC	32.53	32.53	32.53	32.53	32.53	32.53	32.53	32.53	32.53	32.53
MCCPH	101.41	99.84	101.41	105.54	95.046	96.645	101.41	107.77	101.41	93.54
CCS	4.12	.750	4.12	-	4.12	8.895	4.125	4.12	4.125	7.5
SSG	7.5	12	7.5	7.5	13.86	7.5	7.5	1.136	7.5	12
Aspartime	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Fruit flavour	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Mg St	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Total(200 Tab)	150	150	150	150	150	150	150	150	150	150

Ingredients (mg)	A_{11}	A_{12}	A_{13}	A_0
Drug resin complex	32.53	32.53	32.53	32.53
MCCPH 102	102.54	109.290	101.41	113.04
Cross carmellose sodium (CCS)	7.5	0.75	4.125	-
Sodium starch glycollate (SSG)	3	3	7.5	-
Aspartime	3.5	3.5	3.5	3.5
Mixed fruit flavour	0.15	0.15	0.15	0.15
Magnesium stearate	0.8	0.8	0.8	0.8
Total	150	150	150	150

Batches of fast dissolving tablet prepared were A_1 to A_{13}. The formulation A_0 was with taste masked granules without superdisintegrants.

Evaluation of Tablets for post compression parameters [11]

Tablets were evaluated for their physicochemical parameters such as thickness and diameter, weight variation, hardness, friability, assay, disintegration time, wetting time and In Vitro dissolution.

Drug content Determination

Preparation of standard

Ondansetron HCl reference standard (400 µg/ml) was weighed accurately. The drug was dissolved in 0.1N HCl and volume was made upto 100 ml with the same solvent. Then, 1 ml was diluted to 50 ml with the same solvent.

Preparation of sample

Accurately a quantity of the tablet powder (150 mg) from 20 crushed tablets equivalent to 8 mg of the ondansetron HCl was weighed from three different places and then transferred in three 100 ml volumetric flasks. Then, the samples were dissolved in 0.1N HCl and volume was made up to 100 ml using same solvent. The samples were sonicated for about 15 minutes and were then filtered through whatman filter paper. Then the filtrate 5 ml was diluted to 50 ml by using 0.1N HCl. The absorbance of this final solution and standard ondansetron HCl solution were compared at wavelength 310 nm using 0.1N HCl as a blank using UV-visible spectrophometer.

Drug content per/tablet

$$= \frac{\text{Spl Abs}}{\text{Std Abs}} \text{ x } \frac{\text{Std Wt}}{\text{Spl Wt}} \text{ x } \frac{\text{Spl Dil}}{\text{Std Dil}} \text{ x } \frac{\text{Std Potency}}{100} \text{ x Avg. Tab Wt}$$

$$\% \text{ of label claim} = \frac{\text{Qty per tablet}}{\text{Label claim}} \times 100$$

In vitro release study [8]

In vitro drug release was studied using medium 0.1 N HCl, Volume: 500ml, Type I apparatus at 50 rpm and aliquots withdrawn at 10 mins interval.

$$\text{Drug releaser per tablet} = \frac{\text{Spl Abs}}{\text{Std Abs}} \times \frac{\text{Std wt}}{100} \times \frac{1}{50} \times \frac{500}{8} \times \text{potency}$$

RESULTS AND DISCUSSION

Percentage drug loading in DRCs was found from 18.04 to 30.74. The drug-resin with 1:3 ratio treated with 0.1 N HCl -0.1 N NaOH combination gave maximum drug loading i.e. 30.74 %. Therefore, the ratio 1:3 was considered the optimal DRC with complete masking of bitter taste for further studies.

The drug loading in various drug: Resin concentration was found to be 18.85 ± 0.62, 22.84 ± 1.38 and 30.58 ± 1.3 for 1:1, 1:2 and 1:3 respectively. The drug loading is more while increasing the resin concentration, thus the 1:3 ratio was used as optimized ratio.

In similar study conducted by Vijaya Sharma *et al* for taste masking of Levocetrizine with Tulsion 335, drug resin ratio kept constant at 1:3 and stirring time varied from 30 min to 60 min and taste was found to be slightly masked but percentage drug loading increased from 30.15% ± 1.04% for 60 min[59]. In the same experiment activation with drug polymer ratio 1:5 swelling for 30 minutes and activation for 240 minutes resulted 61.4% for acid, 45.80% for alkali and 28.69% of drug loading for acid-alkali activation [12].

Optimization of pH

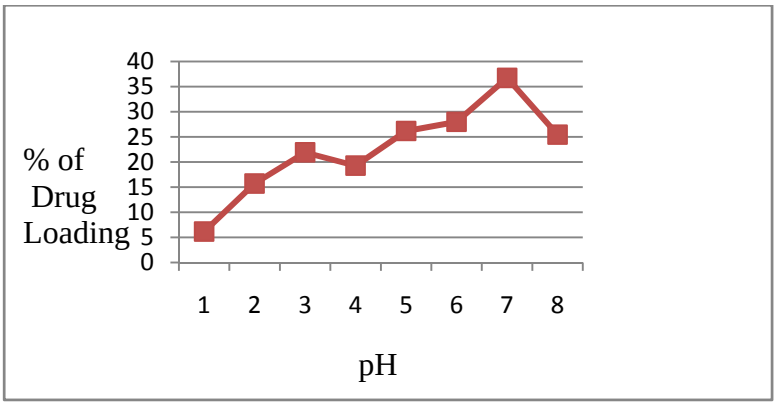

Fig. 1: Effect of pH on percengage of drug loading

Gustatory Sensation Test of DRC

(0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness and 4: strong bitterness); the threshold bitterness concentration being 50µg\ml.

Table1: Gustatory Sensation Test

Volunteer	Bitterness level after						
	5 sec	10 sec	15 sec	30 sec	60 sec	120 sec	180 sec
1	1	1	0	0	0	0	0
2	1	1	0	0	0	0	0
3	0	0	0	0	0	0	0
4	2	1	1	1	0	0	0
5	0	0	0	0	0	0	0
6	1	1	1	0	0	0	0
7	1	0	0	0	0	0	0
8	0	0	0	0	0	0	0
9	1	0	0	0	0	0	0
10	0	0	0	0	0	0	0

Release Profile

Table 2: Percentage Release of Acid, Base and Acid and Base treated Resin

Min	% drug release of 0.1N HCl treated resin	% drug release of 0.1N NaOH treated resin	% drug release of 0.1N HCl and 0.1N NaOH treated resin
2	57.75	70.48	71.23
4	66.25	72.76	76.32
6	71.87	76.14	77.12
8	79.42	79.32	78.34
10	81.10	80.02	82.28

Physical Properties of Tablet Blend

Blends of all formulations showed good flowability (angle of repose <30° and Carr's index ≤12). Bulk densities varied from 0.543 to 0.46 .

Evaluation of physicochemical characteristics and physicomechanical properties

Table 3: Physicochemical and physicomechanical properties of tablet

Wt (mg)	Hardness (kg/cm^2)	Friability (%)	DT (sec.)	Wet Time (sec.)	Assay (%)	Release (%)
146.4 -150.4	3.1-3.3	0.018-0.45	9.5-58.2	83.5-41.0	99.1-101.1	79.2-100.6

Disintegration time

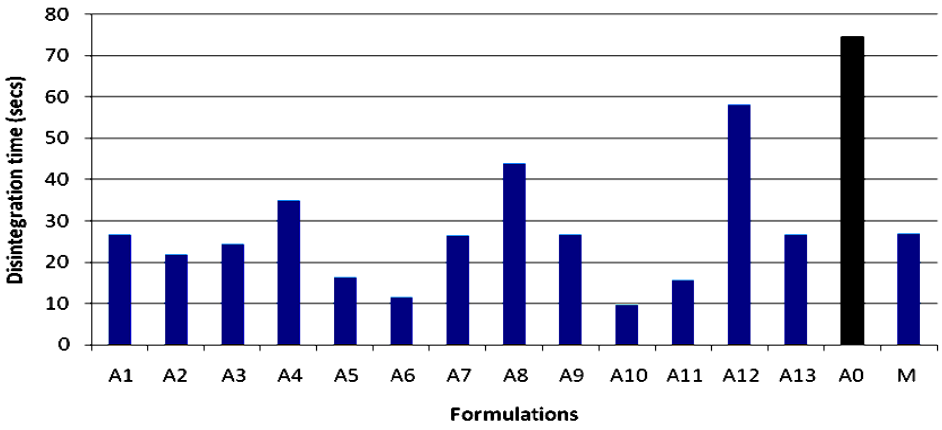

Fig. 2: Disintegration time of formulations

Tablets compressed by direct compression method without any superdisintegrants had wetting time 96.071 seconds and disintegration time 74.47 seconds. When superdisintegrants were used disintegration time decreased. Wetting time and disintegration time of formulations varied with variation in superdisintegrants and their concentration. Batches A_{10}, A_{11} and marketed product have disintegration time of 9.58 seconds and 15.73 and 26.78 seconds respectively.

Wetting Time

Formulation without CCS has higher wetting time 96.07 sec. Addition of CCS in formulation A_1 has decreaed the wetting time to 81.04 sec.

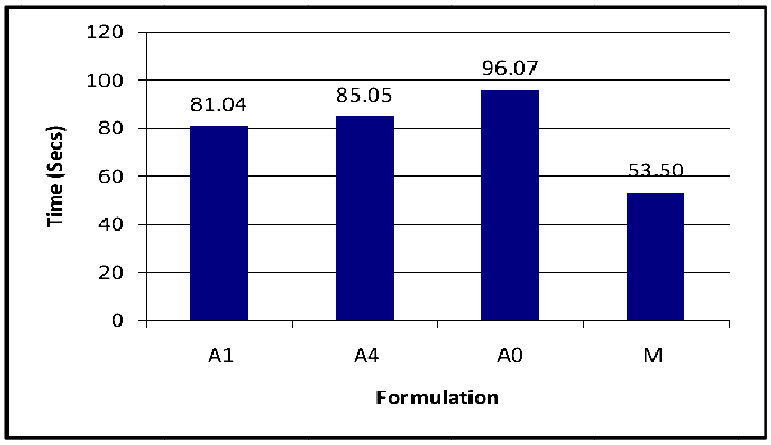

Fig. 3: Effect of CCS on wetting time

Wetting time of formulations was found to be decreased with increasing concentration of SSG.

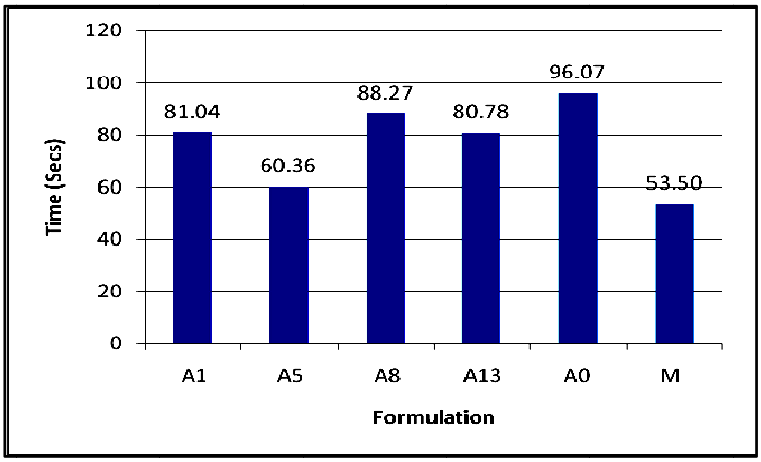

Fig. 4: Effect of SSG on wetting time

Comparative study of superdisintegrants

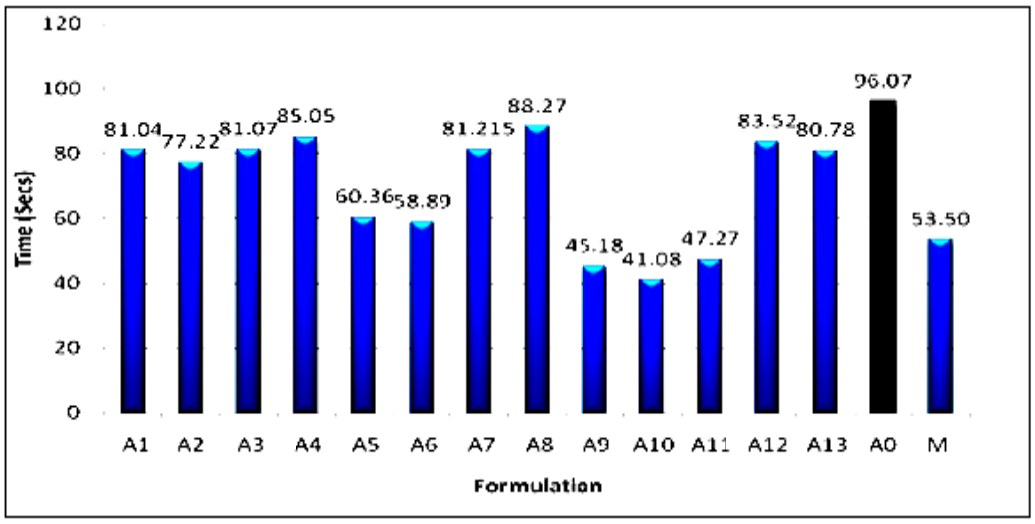

Fig. 5: Effect of superdintegrant on wetting time

In three formulations (A_5, A_6, A_{10} and A_{11}), disintegration time decreased with increase in concentration of croscarmellose sodium but above 5 % disintegration and wetting time remained almost constant. The result suggests that among the different concentration of croscarmellose sodium, the most effective concentration is 5 % which was able to reduce wetting time to 41.08 seconds and 47.27 seconds and disintegration time to 9.58 seconds and 15.73 in formulation A_{10} and A_{11} respectively.

In Vitro Dissolution Studies

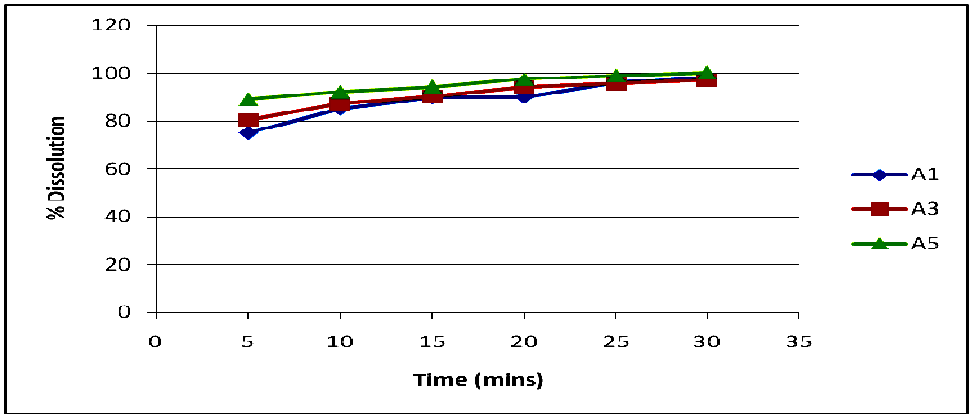

Fig. 6: Dissolution profile of formulations A_1 , A_3 and A_5

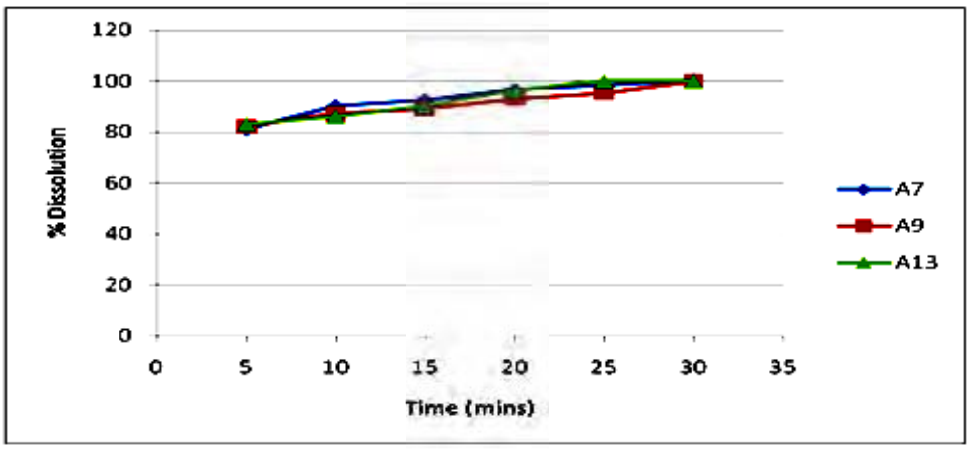

Fig. 7: Dissolution profile of formulations A_7, A_9 and A_{13}

Difference in particle size generated in the disintegrated tablet could affect the drug dissolution since breaking tablet into finer fragments may promote drug dissolution by providing larger total surface area for drug dissolution to take place [16, 18].

Effect of superdisintegrants

Effect of SSG only

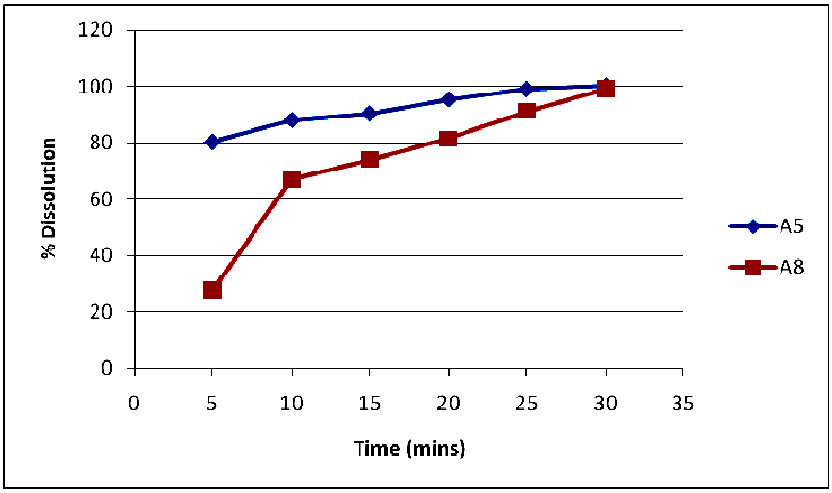

Fig. 8 : Effect of SSG on dissolution

Effect of CCS

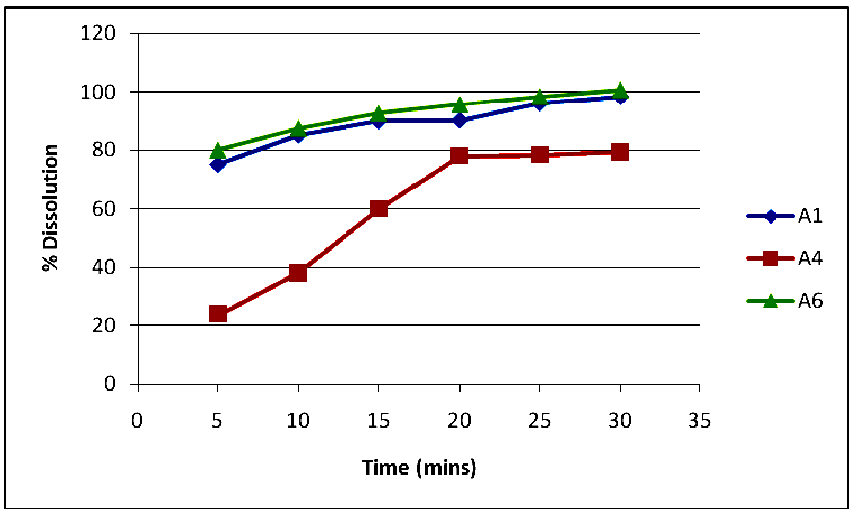

Fig. 9: Effect of CCS on dissolution

It was observed from the results that increasing the concentration of CCS from 0% in batch A_4 to 2.75% in batch A_1 and 5.93 % in batch A_6 has increased the dissolution at 10 minutes from 38.12% in batch A_4 to 85.14% in A_1 to 92.15% in A_6 .Also CCS alone showed maximum dissolution rate with more than 99.13 % drug release in 30 minutes in batch A_8

This shows that the effectiveness of superdisintegrants are in the order of CCS + SSG> CCS > SSG. In all formulations up to 5% w/w concentrations, dissolution rates were increased linearly. Therefore 5% w/w is optimum for all superdisintegrants.

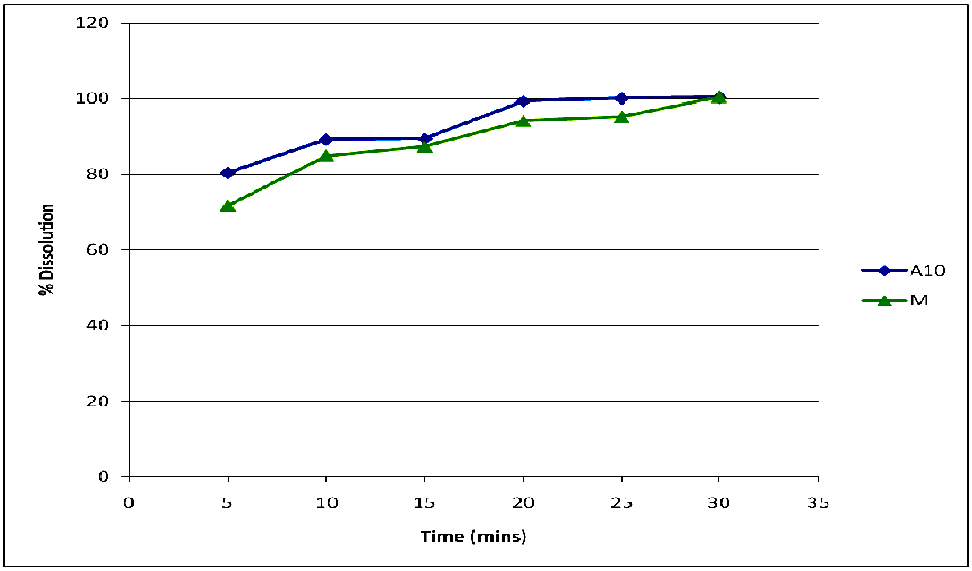

Fig. 10: Comparison of market sample with optimized formulation

Hardness of market sample was 3.987 kg/cm^2. Average wetting and disintegration time was 53.5 and 26.78 secs respectively. The drug release within 10 min was found 84.89 %.

Conclusion

The present study comprises of taste masking of ondansetron HCl using taste masking agent Tulsion 335 and formation of mouth dissolving tablets. Tulsion 335 activated by combined acid and alkali treatment, swollen for 90 min in deionized water, was found to show maximum loading of Ondansetron HCl at pH near neutral.

The most effective concentration found was of croscarmellose sodium and sodium starch glycollate respectively at concentration above 5%. Further, based on the observed result it can be concluded that the unpleasant taste of Ondansetron HCl can be successfully masked by using tulson 335 and Orodispersible tablet of Ondansetron HCl can be successfully prepared by adding superdisintegrant: Croscarmalose sodium and sodium starch glycolate and microcrystalline cellulose PH 102 as diluents using direct compression method.

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