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Formulation Design of Novel Fast Dissolving Tablets Using Low and High Compressible Saccharides

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Abstract: In the present work, fast dissolving tablets of granisetron HCl were prepared using low compressible (mannitol) and high compressible saccharides (sorbitol 5-15% w/w) along with crospovidone, croscarmellose sodium and L-HPC as super-disintegrants in different ratios(2-8% w/w) In case of sorbitol, the presence of interlocking crystals that are generated using specific manufacturing conditions enables strong binding and result in a more robust tablet at low compression forces. In addition, mannitol provides the required dispersibility and mouth feel for a successful FDT formulation. Exhibits significantly low friability, even at a low compression force. In addition contributing to the robustness of the tablets, the sorbitol also imparts a sweet taste and unique textured to the mannitol, thereby improving the ODT formulations mouthfeel. The low level of sorbitol required to obtain an added functionality, mannitol does not affect its pharmacopoeial uniformity to USP-NF standards, thus offering an advantage with respect to the regulatory requirements.

The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity and *in vitro* dispersion time. Based on *in vitro* dispersion time (approximately 12-23 sec), three formulations were selected and tested for *in vitro* drug release pattern (in pH 6.8 phosphate buffer). Short-term stability (at 40º/ 75% RH for 3 months) and drug-excipient interaction (IR spectroscopy). Among the three promising formulations, the formulation containing 8% w/w of crospovidone and 15% w/w of sorbitol, emerged as the overall best formulation ($t_{50\%}$ 3 min) based on the *in vitro* drug release characteristics compared to conventional commercial tablet formulation ($t_{50\%}$ 19.0 min). Short-term stability studies on the formulations indicated that there are no significant changes in drug content and *in vitro* dispersion time ($p<0.05$).

Keywords: Granisetron HCl, fast dissolving tablets, saccharides, crospovidone

Introduction

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus does not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Recent advances in Novel Drug Delivery Systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is "Fast Dissolving Tablets (FDT)[1-4]". Granisetron hydrochloride[5] is a serotonin 5-HT_3 receptor antagonist used as an antiemetic to treat nausea and vomiting following chemotherapy. Its main effect is to reduce the activity of the vagus nerve, which is a nerve that activates the vomiting centre in medulla oblongata. The objective of the present study was to design such a novel drug delivery system for granisetron by simple and cost-effective method having sufficient mechanical integrity, good content uniformity and acceptable palatability.

Materials

Granisetron hydrochloride (GSH) was a gift sample from Natco Pharma Ltd., Hyderabad. Crospovidone (CP) and Croscarmellose sodium (CCS) was gift sample from Wockhardt Research Centre, Aurangabad. Sorbitol was a gift sample from Alkem Laboratories, Mumbai. L-HPC was a gift sample from Arihant Chemicals, Mumbai. Directly compressible mannitol (Pearlitol SD 200) and sodium stearyl fumarate (SSF) were generous gifts from Strides Acrolabs, Bangalore. All the other chemicals used were of analytical reagent grade.

Experimental

Preparation of Fast Dissolving Tablets by Direct Compression Method[6]

Fast dissolving tablets of granisetron hydrochloride (GSH) were prepared by direct compression method according to the formulae given in Table 1. All the ingredients were passed through sieve # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150 mg, using 8 mm round, flat punches on 10-station rotary tablet machine (Clit, Ahemadabad).

Evaluation of tablets

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation[7]. Hardness and friability of the tablets were determined by using Monsanto hardness tester and Roche friabilator respectively. For content uniformity test, ten tablets were weighed and powdered. The powder equivalent to 2.24 mg of GSH was extracted into distilled water and liquid was filtered (Whatmann No. 1 filter paper). The GSH content in the filtrate was determined by measuring the absorbance at 302 nm after appropriate dilution with distilled water. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations[8]. For determination of *in vitro* dispersion time, one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5º and the time required for complete dispersion was determined[9]. IR spectra of GSH and its formulations were obtained by potassium bromide pellet method using Perkin-Elmer FTIR series (Model 1615) spectrophotometer in order to rule out drug-carrier interactions.

Dissolution study[10]

In vitro dissolution of granisetrol HCl fast dissolving tablets was studied in USP XXIII type-II dissolution apparatus (Electro Lab Model TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5ºC as a dissolution medium. IR-spectroscopic studies indicated that the drug is compatible with all the excipients. Short-term stability studies of the above formulations indicated that there are no significant changes in drug content and *in vitro* dispersion time at the end of 3 months period ($p<0.05$).

Stability testing

Short-term stability studies on the selected promising formulations (MCP_3, $MCCS_3$ and ML-HPC_3) were carried out by storing the tablets in amber coloured vial with rubber stopper at 40º/ 75% RH over a 3 months period (as per ICH guidelines). At an intervals of 1 month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

Results and Discussion

Fast dissolving tablets of GSH were prepared by direct compression method employing CP, L-HPC, CCS as super-disintegrant along with low and high compressible saccharides in different ratios. Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance mouth feel. A total of nine formulations and a control formulation MCP_0 (without super-disintegrant) were designed. As the blends were free flowing (angle of repose <30º, and Carr's index <15%) tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specifications i.e., below 7.5%. Drug content was found to be in the range of 98.42 to 99.37%, which is within acceptable limits. Hardness of the tablets was found to be 2.86 to 3.36 kg/cm². Friability below 1% was an indication of good mechanical resistance of the tablets. Among all the designed formulations, three formulations, viz., MCP_3, $MCCS_3$ and ML-HPC_3 were found to be promising and displayed an *in vitro* dispersion time ranging from 12 to 23 sec, which facilitates their faster dispersion in the mouth.

Overall, the formulation MCP_3 containing 8% w/w of crospovidone and 15% w/w of sorbitol was found to be promising and has shown an *in vitro* dispersion time of 12 sec when compared to control formulation (MCP_0) which shows 198 sec for *in vitro* dispersion (Table-2).

In vitro dissolution studies on the promising formulations (MCP_3, $MCCS_3$ and ML-HPC_3), the control (MCP_0) and commercial conventional formulations (CCF) were carried out in pH 6.8 phosphate buffer, and the various dissolution parameter values viz., percent drug dissolved in 5 min, 10 min and 15 min (D_5, D_{10} and D_{15}), dissolution efficiency at 10 min ($DE_{10\ min}$)[11], $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are shown in table 3, the dissolution profiles depicted in Figure 1. This data reveals that overall, the formulation MCP_3 has shown more than six-fold faster drug release ($t_{50\%}$ 3.0 min) when compared to the commercial conventional tablet formulation of GSH ($t_{50\%}$ 19.0 min) and released 4 times more drug than the control formulation in 10 min.

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of MCP_3 showed all the characteristic peaks of GSH pure drug, thus confirming that no interaction of drug occurred with the components of the formulation. Short-term stability studies of the above formulations indicated that there were no significant changes in drug content and *in vitro* dispersion time at the end of 3 months period ($p<0.05$).

Conclusion

The present study conclusively indicates that formulation MCP_3 is very much promising as fast dissolving tablet formulation of granisetron hydrochloride with an *in vitro* dispersion time of 12 seconds and improved mouth feel with good robustness of the tablet.

Table 1: Composition of Different Batches of Fast Dissolving Tablets of Granisetron Hydrochloride

Ingredients (mg/tablet)	Formulation Code									
	MCP_0	MCP_1	MCP_2	MCP_3	$MCCS_1$	$MCCS_2$	$MCCS_3$	$MLHPC_1$	$MLHPC_2$	$MLHPC_3$
Granisetron HCl	2.24	2.24	2.24	2.24	2.24	2.24	2.24	2.24	2.24	2.24
Crospovidone	--	3.0	6.0	12.0	--	--	--	--	--	--
Croscarmellose sodium	--	--	--	--	3.0	6.0	12.0	--	--	--
L-HPC	--	--	--	--	--	--	--	3.0	6.0	12.0
Sorbitol (0-15%)	15.0	7.5	15.0	22.5	7.5	15.0	22.5	7.5	15.0	22.5
Sodium stearyl fumerate	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Talc	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Aspartame	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Flavour	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Mannitol (Pearlitol SD200)	119.26	123.76	113.26	99.76	123.76	113.26	99.76	123.76	113.26	99.76
Total Weight	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**	**150.00**

Table 2: Evaluation of Fast Dissolving Tablets

Parameters	Formulation Code									
	MCP_0	MCP_1	MCP_2	MCP_3	$MCCS_1$	$MCCS_2$	$MCCS_3$	$MLHPC_1$	$MLHPC_2$	$MLHPC_3$
Hardness±SD* (kg/cm^2)	3.30± 0.26	3.16± 0.50	3.36± 0.32	3.03± 0.15	2.90± 0.15	3.00± 0.50	3.00± 0.10	3.03± 0.15	2.86± 0.05	3.36± 0.32
Thickness (mm)	3.15	3.34	3.37	3.25	3.42	3.56	3.18	3.24	3.56	3.15
Friability (%)	0.52	0.45	0.53	0.50	0.50	0.52	0.53	0.45	0.60	0.53
In vitro dispersion time±SD* (sec)	197.75± 2.29	34.73± 2.25	22.93± 2.78	12.47± 1.16	43.63± 1.49	35.44± 1.50	15.64± 0.81	55.19± 0.87	38.71± 1.32	22.69± 1.82
Wetting time* (sec)	199.09± 2.15	34.09± 1.62	25.38± 1.12	14.55± 0.56	44.90± 1.36	36.66± 0.67	17.32± 1.10	58.60± 1.08	39.66± 0.67	25.38± 1.12
Water absorption ratio (%)	55.68± 0.47	74.38± 0.36	87.24± 0.70	96.59± 0.59	71.16± 0.43	72.38± 0.36	94.23± 0.63	69.74± 0.74	74.38± 0.36	89.24± 0.70
Drug content ±SD* (%)	98.78± 0.30	99.33± 1.39	98.42± 0.38	99.07± 0.15	99.37± 0.19	98.95± 0.18	98.91± 0.41	99.48± 0.10	99.07± 0.15	98.61± 0.05
Weight variation	(147 – 154 mg) within the IP limits of ±7.5%									

*Average of three determinations. Formulations MCP_3, $MCCS_3$ and ML-HPC_3 were selected as the best and used for further studies.

Table 3: *In Vitro* Dissolution Parameters in pH 6.8 Phosphate Buffer

Formulation code	D_5 (%)	D_{10} (%)	D_{15} (%)	DE_{10} min (%)	$t_{50\%}$ (min)	$t_{70\%}$ (min)	$t_{90\%}$ (min)
MCC_0	12.00	20.00	25.00	10.44	>30	>30	>30
MCP_3	60.00	90.00	100.00	58.08	3.00	7.00	10.00
CCF	17.00	32.00	46.00	16.52	19.00	>30	>30

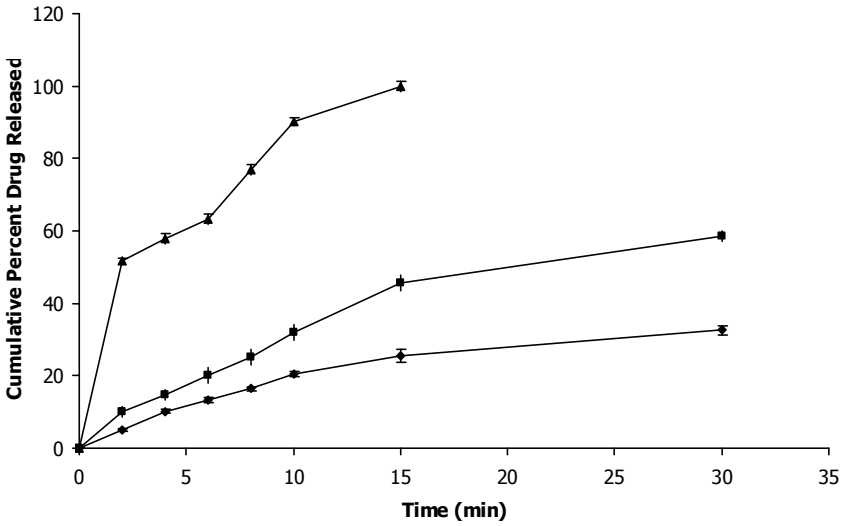

Figure 1: *In vitro* cumulative percent drug release versus time plots of promising formulations in pH 6.8 phosphate buffer.(Plot showing percent cumulative release of promising granisetron HCl formulations.)
MCP_0 (–♦–), CCF (–▲–), MCP_3 (–■–)

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References

1. Seager H. Drug delivery products and the Zydis Fast Dissolving Dosage Forms. J Pharm Pharmacol, 1998, 50, 375-82.
2. Chang RK, Guo X, Burnside BA, Cough RA. Fast dissolving tablets. Pharm Tech, 2000, 24(6), 52-8.
3. Dobetti L. Fast-melting tablets: Developments and Technologies. Pharma Tech, 2001, (Suppl.), 44-50.
4. Kuchekar BS, Arumugam V. Fast Dissolving Tablets. Indian J Pharm Educ, 2001, 35, 150-2.
5. Sweetman SC (editor). Martindale: The Complete Drug Reference, 35th edition. London, Pharmaceutical Press, 2007, p. 1562.
6. Kaushik D, Dureja H, Saini TR. Formulation and evaluation of olanzapine mouth dissolving tablets by effervescent formulation approach. Indian Drugs, 2004, 41, 410-2.
7. Banker GS, Anderson NR. Tablets. In: Lachman L, Liberman HA, Kanig JL (editors), The theory and practice of industrial pharmacy, 3rd ed. Mumbai, Varghese Publishing House, 1987, p. 293-9.
8. Indian Pharmacopoeia: Controller of Publications, Govt. of India, Ministry of Health & Family Welfare, New Delhi, 1996, p. 735-6.
9. Bi YX, Sunada H, Yonezawa Y, Danjo K. Evaluation of rapidly disintegrating tablets by direct compression method. Drug Develop Ind Pharm, 1999, 25(5), 571-81.
10. Bhagwati ST, Hiremath SN, Sreenivas SA. Comparative evaluation of disintegrants by formulating cefixime dispersible tablets. Indian J Pharm Educ Res, 2005, 39(4), 194-7.
11. Khan KA. The concept of dissolution efficiency. J Pharm Pharmacol, 1975, 27, 48-9.

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