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DESIGN AND EVALUATION OF CONTROLLED RELEASE RANITIDINE HYDROCHLORIDE TABLETS USING DIFFERENT GRANULATION METHODS

K.K. Singh, Suvarna S. Somade

*C.U. Shah College of Pharmacy, S.N.D.T. Women's University, Mumbai, Maharashtra, India 4000049
sirjiwan@vsnl.com*

ABSTRACT SUMMARY :

Controlled release ranitidine hydrochloride matrix tablets have been developed using direct compression, wet granulation, and pelletisation by extrusion spheronization methods. The tables showing prolonged & consistent in-vitro drug release upto 14-16 h have been obtained. A much higher polymer concentration was required in case of wet granulation method as compared to direct compression and pelletisation to achieve desired release profile.

KEY WORDS:

Controlled release, oral drug delivery, hydrophilic matrices.

INTRODUCTION:

Ranitidine hydrochloride, a competitive and reversible histamine H₂-receptor antagonist, is a widely used anti-ulcer drug. It is safe, low molecular weight drug with biological half life of 2.5-3h. Conventional dose of 150 mg has demonstrated inhibition of gastric acid secretion after 5h but not after 10h1. An alternative bed time dose of 300 mg might lead to plasma fluctuations, thus making controlled release dosage form of ranitidine desirable.

Various processing methods like wet granulation, spray drying, fluidized bed granulation etc. have been employed to prepare granulations. Quantitative and physico-chemical measurements are applied to pharmaceutical granulations to achieve rational selection of a particular method.

The present work reports the comparative evaluation of conventional wet granulation, pelletisation and direct compression methods for development of controlled release ranitidine hydrochloride tablets.

EXPERIMENTAL METHODS:

Three different viscosity grade of HPMC viz. K100M, K15M and K4M were used as release retardants. Avicel PH 101, lactose and magnesium stearate were used as excipients. Granulations were prepared using six different drug : polymer ratios (3:4, 3:3, 3:2.5, 3:2, 3:1.5 & 3:1) for each of the polymer, keeping average weight of tablet constant for all formulations.

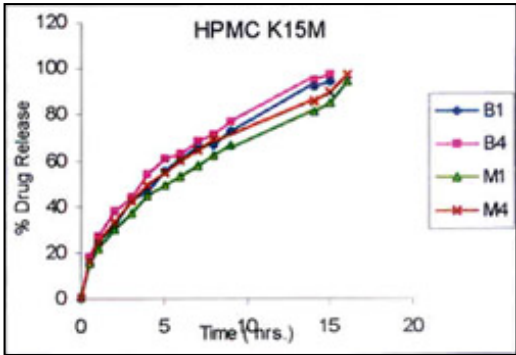
Drug and matrix materials were blended for direct compression and granulated using absolute ethanol for wet granulation method. The extrusion spheronisation process was optimized for formulation and process variables². Drug and matrix materials were kneaded using absolute ethanol and extruded through 16 mesh screen. Cylindrical segments formed were immediately rotated on a spheronizer to obtain good pellet characteristics. To get smooth, unspitted surface of tablets³ and reduced air entrapment in voids among the pellets, satisfactory pelletised granulations, containing about 30% w/w of pellets in 16-22 mesh fraction and 35% w/w of pellets in 22-36 mesh fractions were used.

Blends/ dried granules / pellets were evaluated for flow properties and % compressibility. Tablets were evaluated for % swell, hardness, friability, drug content and drug dissolution, In-vitro dissolution was performed in USP XXIII apparatus Type II, using both pH7.2 buffer and by pH change method. Ranitidine hydrochloride being moisture sensitive, selected tablet formulations were film coated with Instacoat Moistshield ICMS-251 in non-aqueous solvent system and studied for stability.

RESULTS AND DISCUSSION:

For HPMC K15M, wet granulated tablets containing the drug : polymer ratio of 3:4 released the drug at the rate of 81.97 mg /h^{1/2} with t_{90%} of 13.5h, as compared to pelletised tablets containing the same 3:4 drug : polymer ratio which released the drug at slower rate of 72.88 mg/h^{1/2} with t_{90%} of 16.6 h. A much lower drug : polymer ratio of 3:2:5 retarded the drug release for a longer period of time in case of pelletisation (78.6 mg/ /h^{1/2} with t_{90%} of 14.0h) as compared to 3:4 in case of wet granulation. (Fig1)

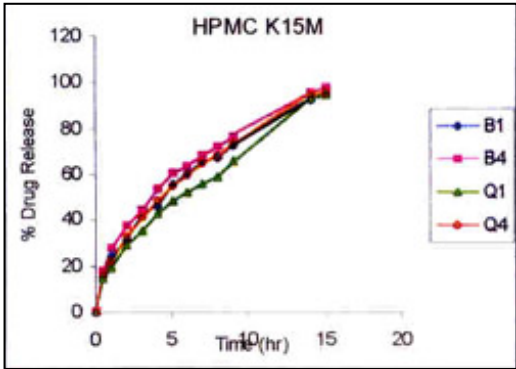
Fig 1 Effect of drug : polymer ratio on dissolution of wet granulated and pelleted tablets.



- B1 : Wet granulation (3:4)
- B4 : Wet granulation (3:2:5)
- M1 : Pelletisation (3:4)
- M4 : Pelletisation (3:2:5)

Directly compressed tablets containing 3:2:5 drug : Polymer ratio had an almost similar drug release profile (82.76 mg/h/1/2 with t90% of 13.2h) as compared to drug : polymer ratio of 3:4 in case of wet granulation.

Fig 1 Effect of drug : polymer ratio on dissolution of directly compressed and wet granulated tablets.



- B1 : Wet granulation (3:4)
- B4 : Wet granulation (3:2:5)
- Q1 : Direct Compression (3:4)
- Q4 : Direct Compression (3:2:5)

Fig 3 shows the photographs of directly compressed tablets of ranitidine hydrochloride at different time intervals during in vitro dissolution studies. The tablets were found to swell gradually with time and formed hydrated swollen matrix. The transverse section of tablets at 8 h, revealed intact drug core as shown in fig 4. Similar results were observed with wet granulation and pelletisation.

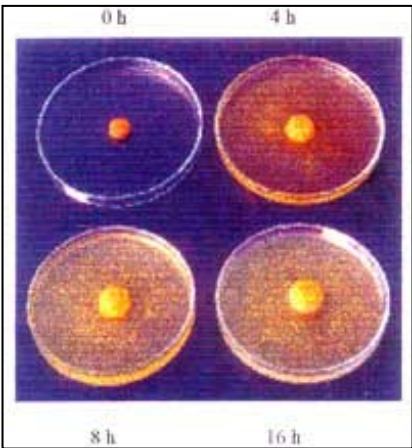


Fig.3 Photographs of directly compressed tablet at 0h, 4h,8h, 16h time period during in-vitro dissolution studies.

The present swell increased with increase in polymer concentration, irrespective of granulation method used.

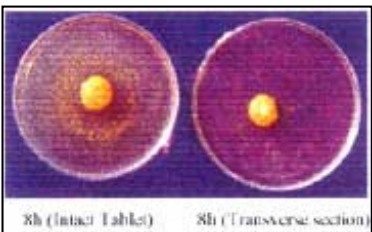


Fig.4 Intact tablet and Transverse section of tablet at 8h, during dissolution studies.

Thus drug : polymer ratio and granulation methods had a significant effect on *in-vitro* dissolution profile. A much lower concentration of polymer was required in case of direct compression and extrusion spheronisation methods, as compared to wet granulation method to achieve desired dissolution profile.

Similar observations were made with other two viscosity grade of HPMC. However, for all the granulation methods, higher viscosity grade of polymer and higher drug : polymer ratio retarded the drug release for longer period of time. All the formulations showed matrix diffusion controlled drug release.

The process of wet granulation resulted in better flow properties & less percentage of fines as compared to direct compression method, whereas an advanced method of wet granulation viz. extrusion spheronisation had added advantages of reduced drying time, excellent flow properties and reduced drug : Polymer ratio for desired *in-vitro* drug release. Direct compression method with fair to passable flow properties of blends, had advantages of reduced processing steps and time, reduced drug : polymer ratio for desired release profile and good stability as compared to wet granulation and extrusion spheronisation methods.

CONCLUSION :

In conclusion, use of direct compression and extrusion spheronization method resulted in prolonged and consistent drug release at lower polymer concentrations, as compared to wet granulation for preparation of controlled release ranitidine hydrochloride tablets.

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