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DEVELOPMENT OF CONTROLLED RELEASE ANTIULCER TABLETS USING EXTRUSION- SPHERONIZATION METHOD AND STUDY OF EFFECT OF HYDROPHILIC POLYMERS ON RELEASE RATE AND *IN VITRO* EVALUATION

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ABSTRACT

The purpose of the present investigation was to develop controlled release ranitidine hydrochloride swelling matrix tablets using extrusion spheronisation method and HPMC K100M as release retardant, for once a day administration. This study evaluated the effects of formulation and process variables on the properties of pellets and the tablets were compressed from essentially spherical, free flowing pellets. Main effects related to excipients, extruder screen size, spheronizer speed and residence time were studied. Optimum parameters were selected to get pellets of good flowability, % sphericity, desired particle size distribution and best possible yield. Experiments demonstrated that changes in content of granulating agent, spheronisation speed and residence time can result in marked differences in the shape and percentage yield of spheroids in different size ranges. All the tablet formulations showed prolonged and consistent *in-vitro* drug release up to 17 -20 hours, the rate of drug release was diffusion controlled and follows Higuchi model. Higher polymer concentration retarded the drug release for longer period of time.

KEYWORDS: Controlled release, Extrusion spheronisation, Ranitidine hydrochloride, Formulation and process variables, Hydrophilic matrix tablet.

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INTRODUCTION

Extrusion- spheronization is a versatile process capable of producing granules or spheres having unique physical properties. Pellets, for pharmaceutical purposes, range in size, typically from 0.5 to 1.5 mm. The major advantage of extrusion – spheronisation method over other methods of producing drug loaded spheres or pellets is the ability to incorporate high levels of active components without producing an excessively large particle and provide a high degree of flexibility during the design and development of oral dosage forms. Celik and Maganti compared the compaction behaviour of MCC pellet formulations to that of powders and found significant differences. Formulation of drugs in the form of pellets filled in capsules or compressed into tablets offers flexibility as to target release properties[1]. Pellets have been used to obtain controlled drug delivery using different polymers as release retardants [2]. The characteristics of pelletized product are greatly affected by formulation and process variables [3]. Literature reveals that tablets have been compressed from essentially spherical and free flowing pellets and effects of certain process variables on tablet properties have been studied by Malinowski and smith [4]. The spheres with good deformation and bonding characteristics result in tablets having desirable physical properties. The tablet characteristics can be modified by altering either the composition of the spherical particles[5], granulating fluid [6] or the processing conditions [4]. The present investigation was carried out to develop a matrix type controlled release tablets of ranitidine hydrochloride, for once a day administration using HPMC K100M, K15M and K4M (Methocel ^{TM}) as release retardants. The composition and process conditions were optimized to obtain pellets of smooth surface, good flowability, % sphericity and desired particle size distribution. The pellets were further compressed into tablets and evaluated. Ranitidine hydrochloride, widely used anti-ulcer drug is a H_2 receptor antagonist with short biological half life of 2.5 – 3h [7]. In ulcer patients, the gastric pH is lowered to 1-3 and after ulcer treatment with conventional ranitidine dose, blood level concentration above 120-150 ng/ml provides pH above 3.5 for short period of time. Conventional clinical doses of 150 mg ranitidine twice daily is not effective in controlling day time acidity as compared to 300 mg dose at bed time in duodenal ulcer patients [8]. An alternative bedtime dose of 300 mg may lead to great amount of plasma fluctuations thus indicating need for development of controlled release dosage form of ranitidine. Short biological half life of drug also favors development of CR formulation. The desired controlled release formulation will provide therapeutic blood levels with minimum plasma fluctuations and maintenance of pH about 4-6 for longer period of time. It will also provide advantages of reduced side effects, reduced frequency of dosage administration and better patient compliance.

Literature has revealed sustained release dosage forms of ranitidine hydrochloride employing bilayer technology[9] and gastroretentive drug delivery approaches [10,11]. Bilayer tablet comprises one layer formulated for immediate release (IR- 150 mg ranitidine) and second layer formulated for sustained release (SR- 150 mg). Saha and Pal have prepared ranitidine microcapsules with biphasic release kinetics [11]. Multiunit floating system using lipid carriers was developed by melt granulation technique and evaluated for in vitro floating and drug release [12]. Physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying, leads to incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window, especially in the upper part of the small intestine; once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The drug should have absorption window either in the colon or throughout the gastrointestinal tract for complete absorption. Ranitidine is

absorbed only in the initial part of small intestine and shows 50 % absolute bioavailability [13,14]. Hence a beneficial delivery system for Ranitidine would be one which not only controls the drug release but also possesses the ability to control and prolong the gastric emptying time and can deliver drug in sufficient concentrations to the absorption site (i.e. upper part of the small intestine). The clinically acceptable SR dosage forms of ranitidine prepared with conventional technology may not be successful in controlling gastric residence time and drug release both, thereby providing reduced efficacy of administered dose. Several approaches are currently used to prolong gastric retention time such as polymeric bioadhesive systems [15], hydrodynamically balanced systems [16], high density formulations [17], swelling and expanding systems [18]. The purpose of present investigation was to develop gastroretentive swelling matrix systems of Ranitidine hydrochloride that will release drug consistently upto 17-20 h. Multiunit dosage forms such as pellets and granules were found to be more suitable because they claim to reduce the intersubject variability in absorption and lower the probability of dose dumping [19]. The pellets compressed into tablets or filled into capsules offer additional advantages of dosage accuracy and ease of administration. Further a single HPMC matrix tablet undergoes significant swelling after oral administration, inhibits gastric emptying and releases the drug continuously for prolonged time. The adjustment of polymer concentration,viscosity grade and addition of different types and amounts of excipients to HPMC matrix can modify the drug release rate [20,21]. In general, these formulation variables and processing factors affect drug release profiles. Thus the present investigation applied a systematic and novel approach of compressing pellets into swelling matrix tablets to deliver Ranitidine hydrochloride continuously in a sustained manner and to improve efficacy of the drug.

MATERIALS AND METHODS

Ranitidine hydrochloride was received as a gift sample from Unichem Laboratories Ltd. Mumbai, India. Hydroxy propyl methyl cellulose (Methocel^{TM} K100M, K15M, K4M) polymer and Avicel PH 101 were supplied by Colorcon Asia Pvt. Ltd. and Signet Chemicals, Mumbai respectively. Coating materials provided by Ideal cures Ltd., Mumbai. All other chemicals were of either laboratory reagent or analytical reagent grade.

A. Preparation and Evaluation of pellets

Extrusion-spheronization was evaluated as a granulation technique to obtain desired pellet characteristics for preparation of RH matrix tablets. The first step in this process was to study the effect of the formulation and process variables on pelletized product characteristics [22], so as to get pellets with best possible yield, good flowability and desired particle size distribution [23,24]. Three different viscosity grades of HPMC (HPMC K 100 M, K 15M, K 4M) were used as release retardant and Avicel PH 101, lactose and magnesium stearate were used as excipients. Ranitidine hydrochloride equivalent to 300 mg of ranitidine and 6 different drug: polymer ratios viz 3:1, 3:1.5, 3:2, 3:2.5, 3:3, 3:3.5 and 3: 4 for each of the polymer were used; keeping average weight of the tablet constant. All materials (Batch size-150 gm) except magnesium sterate were blended in a polybag using geometric dilution principle and kneaded into wet mass of required plasticity using distilled ethanol as granulating agent in a kalweka planetary mixer and the cohesive mass was extruded through 16 mesh sieve so that screen was not blocked and extrudates of length 0.2 to 0.4 cm were obtained. The extrudates were immediately rotated on a laboratory bench top multibowl spheronizer MBS 120, fitted with 1 mm cross hatch pattern friction plate, using optimum process conditions of spheronizer speed of 900 rpm and residence time of 5 min. Lubrication was done using Mg stearate during spheronisation for 1 minute using magnesium stearate, to avoid sticking and facilitate smooth discharge of pellets from spheronizer. The pellets obtained were dried on paper lined trays in hot air oven at 45^0 for 1 h. Spheroids were then

dried and evaluated for surface texture, angle of repose, bulk density (BD), tapped density (TD), Carr's index (I_c), Hausner's ratio (H) and % sphericity[15,16] as follows. Surface texture was determined by optical microscopy. The angle of repose, which measures the resistance to particle flow was determined by fixed funnel method, using equation: Tan θ = 2H/D Where 2H/D is the surface area of the free standing height of the heap that formed after making the pellets flow from glass funnel. Tapped density and Bulk density of matrix pellets was determined using tap density apparatus. Carr's index and Hausner's ratio were determined using the following equations. Carr's index (I_c) = TD – BD / TD Hausner's ratio (H_g) = TD/BD Percent sphericity was determined by tracing the pellets (magnifacation 45x) on a block paper using camera lucida (model-Prism type, Rolex, India) and circulatory factor was calculated using equation : $S= p^2 / (12.56 \times A)$ where A is area (cm^2) and p is perimeter (cm).

B. Optimization of formulation variables

Different excipients were tried viz. lactose, dicalcium phosphate, and mixture of Avicel PH 101 and lactose in a ratio of 1:1 for optimization of formulation variables. Effect of these diluents on pellet characteristics such as surface texture, percentage sphericity, flowability and % w/w yield in different size ranges i.e. 16-22 # fraction (x), 22-36 # fraction (y) and 36-80 # fraction (z) was determined (Table 1). Effect of volume of the granulating agent was also determined on the pellet characteristics (Table 2).

C. Optimization of process variables

Extrusion-spheronisation was further optimized for process variables, keeping formulation variables constant. Process variables such as extruder screen size, spheronization speed and residence time (Tables 3, 4) were studied. Extrusion was carried out using different mesh screen viz. 16, 22 and 36. Percentage sphericity and % w/w of different sieve fractions were determined. Spheronization was carried out at variable friction plate speeds viz. 600, 900, 1100 rpm for different residence time until pellet bed rotated axially and showed good fluidization. Shape of spheroids and % w/w fractions of different size ranges were determined.

D. Formulation of controlled release tablets using pellets

Free flowing pellets of different compositions containing various drug:polymer ratios were prepared using optimum formulation and process parameters (Table 5). The pellets of various compositions containing 3 different viscosity grades of HPMC were evaluated for physical properties (Table 6,7). The tablets were compressed from these pellets on a single punch tablet machine (Royal artist, India) using 18.6 mm x 8 mm caplet shaped concave punches, keeping a target weight of 750 mg. As compression of 1 mm size spheroids with smooth surface texture and good flowability resulted in tablets with pitted surface, it was decided to use blend containing certain percentage of fine spheroids. Compression of 30-35% w/w of spheroids of each of 0.71 - 1 mm size and 0.42 - 0.71 mm size and 30-35 % of spheroids of 0.18 – 0.42 mm size resulted in tablets with smooth, unpitted surface. Therefore, spheroids in these proportions and size ranges were prepared and then used for compression into tablets. Ranitidine being a moisture sensitive drug, was processed under controlled conditions of temperature and humidity [25]. Preparation of pellets and compression into tablets was carried out at low temprature (<25°C) and < 50 % RH.

E. Evaluation of controlled release tablets

The tablets were evaluated for hardness, friability and drug content as per official pharmacopoeial methods and percentage swell of tablet was determined periodically by determining increase in weight of tablet during dissolution study using following formula.

$\% \text{ Swell} = (W_t - W_0) / W_0 \times 100$

Where W_t - Weight of tablet after swelling at different time interval

W_0 - Initial weight of tablet

In vitro dissolution studies of compressed tabletsThe release rate of the drug from the tablets was determined (n=3) using USP XXIII, Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of phosphate buffer pH 7.2 at 37 ± 0.5°C and 50 rpm. The sample (5ml) of solution was withdrawn from the dissolution apparatus at one hour intervals and replaced with fresh dissolution medium. Samples were filtered through 0.45 µm membrane filter and diluted to suitable concentration using phosphate buffer. The samples were analysed using UV-VIS spectrophotometer (Shimadzu UV) at 315 nm. Cumulative percentage drug release was calculated using an equation obtained from standard curve (Table 8).

RESULTS AND DISCUSSION

The influence of various formulation and process parameters on physicochemical properties of pellets have been studied. The effect of different drug : polymer ratios and polymer viscosity on dissolution of tablets compressed from pellets was also observed. Selection of appropriate excipients is necessary as they impart spheronization capacity to drug and bring about formation of pellets of suitable strength and integrity[12]. The diluents used and amount of granulating agent had prominent effect on the spheronization of extrudates. Use of dicalcium phosphate resulted in rough, irregular surface of spheroids and greater proportion of pellets of very small size as compared to other fillers. Rough surface may be attributed to brittle and insoluble nature of dicalcium phosphate[26]. Mixture of Avicel PH 101 and lactose (1:1 ratio) was found to be best as complete spheroids of smooth surface and good % sphericity were obtained(Table 1). Avicel (MCC) and lactose provide cohesiveness to wet mass, retain large quantity of binding agent and show good extrusion behaviour at optimal concentrations. MCC confers a degree of plasticity to wet mass and enhances spheronization This consequently leads to spherical, and hard spheroids with smooth surface texture. The amount of liquid and its distribution in the wetted mass are important factors because the liquid phase also contributes to the desired plasticity[6]. Ideally liquid content should be high enough to impart optimum plasticity however, it should not make the mass very wet, causing adhesion of extrudates which makes further processing impossible. As ranitidine hydrochloride is a moisture sensitive drug, optimum amount of distilled ethanol was used as the granulating agent. The increase in a quantity distilled ethanol resulted in bigger rods after extrusion due to better cohesion and so less percentage of fine spheroids after spheronization (Table 2). Further increase in amount (200 ml) led to 55 % w/w spheroids of size range 0.425 to 1.0 mm, 5 % of spheroids of size > 1mm and reduced % yield of only 60 % . The greater variation in spheroid size and reduced total yield were obtained because higher amount resulted in very wet mass and adhesion of extrudates to sides of spheronizer.

Extrudates of length 0.4 to 0.6 cm using moderate amount (150 ml) of granulating agent, resulted in maximum % w/w spheroids of 1mm size with 91% sphericity at 900 rpm and 5min residence time. However compression of these 1 mm size spheroids resulted in tablets with pitted surface. This is in accordance with earlier observations by Milli and Schwartz [6], Alderaborn and Wikberg [27] where compacts of 1mm spheroids resulted in tablets with pitted surface and the individual compressed spheroid could clearly be distinguished at the tablet surface. The extrudates of length 0.2 - 0.4 cm using 120 ml ethanol, when spheronized, resulted in good spheroids with 91-93% sphericity and better total yield. Further spheroids in different size ranges viz. 27-30% w/w of spheroids of each of 0.71-1 mm size (x) and 0.42-0.71 mm size (y) and 30-35 % of spheroids of 0.18-0.42 mm size (z) were obtained. Compression of such granulation containing three different size ranges of spheroids resulted in tablets with smooth, unpitted surface. Fine spheroids (z) which fill up the voids among bigger pellets during compression may be responsible for unpitted tablet surface and improved elegance. The theoretical void space of powder of uniform spheres in closet packing

is 26 %. The filler excipients can be either primary powder particles or can be in the form of secondary agglomerates, such as granules or pellets and use of pellets is preferred to reduce the risk of segregation [28]. Smaller size spheroids (y,z) provide cushioning effect and prevent fusion of adjacent pellets. Spherical pellets as filler also possess advantages such as lowest surface area to volume ratio, good flow properties and uniformity in packing [29], which are important factors to achieve uniformity of weight and drug content in final tablet formulation. Thus the use of different proportions of spheroids in different sizes can be justified for compaction of uncoated pellets of drug. Optimization of formulation variables showed that use of a mixture of Avicel PH 101 and lactose (1:1 ratio) and optimum amount of distilled ethanol that produce good spheroids in these proportions and size ranges may result into hard and elegant tablets.

Table 1
Effect of diluents on pellet characteristics

Pellet Characteristics	Diluents		
	Lactose	Dicalcium phosphate	Avicel PH 101 + Lactose (1 : 1)
Surface Texture	Smooth	Rough	Smooth
% Sphericity			
0.710-1.0 mm (x)	89 %	85 %	93 %
0.425-0.71mm (y)	91 %	89 %	94 %
0.18-0.425mm (z)	93 %	91.5%	92 %
% Yield in (x)	20 %	15 %	28 %
size range (y)	20 %	20 %	30 %
(z)	45 %	50 %	30 %
Flowability	Good	Fair	Good

Note: (Spheronisation speed-900 rpm , spheronisation time-5 min and batch size-150g.)
(x) = 0.710-1.0 mm i.e. 16-22 # fraction, (y) = 0.425-0.71 mm i.e.22-36 # fraction
(z) = 0.180-0.425 mm i.e. 36-80 # fraction

Table 2
Effect of volume of granulating agent on pellet characteristics

Ethanol Used (ml)	Extrudate Characteristics	Pellet Characteristics	
		% w/w of Spheroids	% Sphericity
120	Rods of short length 0.2-0.4cm.	(x)=32.5 % (y)=27.2 % (z)=29.3 %	92 %
150	Rods of length 0.4-0.6cm	(x)=62.5 % (y)=12.5 % (z)=2 %	91 %
200	Rods of length 0.6-0.8cm	(x)=35 % (y)=20 % (z)=2 % >1mm=5%	93 %

Note: (x) = 0.710-1.0 mm i.e. 16-22 # fraction, (y) = 0.425-0.71 mm i.e.22-36 # fraction
(z) = 0.180-0.425 mm i.e. 36-80 # fraction

The study of effect of process variables showed that the extrusion through 22 and 36 mesh sieves gave higher percentage of spheroids in smaller size range(< 0.42mm). Extrusion of wet mass through 16 mesh screen was found to give desired mix of spheroids in three different size ranges (Table 3) and selected for extrusion.

Optimization study of spheronization speed and time showed that lower spheronization speeds of 300 and 600 rpm resulted in incomplete spheronization with rods and dumbbells. The higher speed of 1100 rpm led to greater proportion of smaller spheroids of size 0.18-0.42 mm. Variable spheronization speeds and time resulted in an incomplete process and reduced percent yield (Table 4). Spheronization speed of 900 rpm was found to be optimum condition to produce discrete, spherical, hard and free flowing good pellets of desired sizes and proportions. Spheronization time also affects on the pellet shape and size[23,24]. Increase in the residence time from 3 min to 5 min at 900 rpm resulted in increased % sphericity from 85% to 95 %. Thus in case of process variables, extrusion of wet mass through 16 mesh screen and spheronisation of extrudates at 900 rpm for 5 mins time period were found to produce spheroids in desired different size ranges, with good % sphericity for preparation of controlled release ranitidine hydrochloride matrix tablets. Formulations L_1-L_7 , M_1- M_7 , N_1- N_7 containing HPMC K100M, K15M , K4M respectively were prepared using extrusion – spheronization method (Table 5) and then compressed into tablets. Pellets were evaluated for physico- chemical properties and results of evaluation have been reported in Table 6. Angle of repose (θ°) for the pellets was in the range of 22-26°, and Hausner's ratio was < 1.25 indicating good flow potential for compositions (Table 6, 7). The measured tapped density 0.57 to 0.68 g/ cm^3, Carr's index 8.6 to 13.8 % were well within limits indicating good flowability. Flowability was found to decrease as the polymer concentration was increased from formulation L_1 (3:1 ratio) to formulation L_7 (3:4 ratio). Gradual decrease in % sphericity and % yield of pellets was observed as the polymer concentration was increased. This may be due to decrease in amounts of Avicel and lactose in formulations containing higher polymer concentration to keep tablet weight constant. All the formulations were found to possess excellent compressibility in range of 9 to 14. Thus drug : polymer ratio and other excipients used in formulations affects on the flow properties and pellet characteristics, irrespective of viscosity grade of HPMC. The pellets were compressed and evaluated for weight variation, hardness, friability, drug release, % swell and drug content. Tablets had low friability (0.2-0.4%) and hardness was in the range of 7-9 kg/cm^2. The drug content was found to comply with pharmacopoeial requirements (97.5-102.5%). Irrespective of the viscosity grade of HPMC used, as the polymer concentration was increased, % swell value was found to increase.

Table 3
Effect of extruder screen size on pellet characteristics

Extruder Screen Size	Sieve Fraction (% w /w)	% Sphericity
16# (1 mm)	16-22 # - 32 .0 % 22-36 # - 25 .0 % 36-60 # - 27 .0 % 60-80 # - 6 .0 %	91 %
22# (0.71 mm)	22-36 # - 35.8 % 36-60 # - 46.5 % 60-80 # - 10 .0 %	91 %
36# (0.42 mm)	36-60 # - 51.2 % 60-80 # - 38.5 % 80-100# - 8 .0 %	93 %

Table 4
Effect of spheronization speed and time on pellet characteristics (Batch size = 150 gms.)

Speed (rpm) and time	Status of Spheronization	Pellet Characteristics	
		% w/w	% Sphericity
300 (3min)	No Spheronisation, Rods.	-	-
600 (3min)	Incomplete, dumbell and Ellipsoid shaped pellets.	(x)=20 % (y)=30 % (z)= 20%	-
600 (5 min)	Ellipsoids	(x)=20 % (y)=15 % (z)= 30%	80-85%
900 (3min)	Complete, Good Spheroids.	(x)=35 % (y)= 30 % (z)= 25.3%	85 -90 %
900 (5min)	Complete, Good Spheroids.	(x)=32.5 % (y)=27 % (z)= 29.3 %	95 %
1100(3min)	Complete, Good Spheroids.	(x)=18% (y)=35 % (z)= 43%	93 %
600-1min 900-1min 1100-1min	Higher proportion of fines	(x)=24 % (y)=20% (z)= 8%	Wide Variation
600-1min 900-2min	Incomplete spheronisation. Reduced total yield.	(x)=18 % (y)=5 % (z)= 2%	Wide Variation
600-2 min. 900-3min.	Incomplete, Ellipsoid and Dumbell shaped pellets.	(x)=27 % (y)=20 % (z)= 25% >1 mm.=10 %	85-89 %
600-1 min. 900-2 min. 1100-2 min.	Ellipsoids & Spheroids Ellipsoids & dumbells	(x)= 40 % (y)=26 % (z)= 20 %	-

Note: (x) = 0.710-1.0 mm i.e. 16-22 # fraction, (y) = 0.425-0.71 mm i.e.22-36 # fraction (z) = 0.180-0.425 mm i.e. 36-80 # fraction

Table 5
Formulae for preparation of pellets

Formulation (mg)	M_1	M_2	M_3	M_4	M_5	M_6	M_7
Ranitidine HCL	336	336	336	336	336	336	336
HPMC K15M	100	150	200	250	300	350	400
Avicel PH101	200	200	150	110	55	50	5
Lactose	60	60	60	50	55	10	5
Magnesium Stearate	4	4	4	4	4	4	4
Tablet Weight	700	750	750	750	750	750	750

L_1–L_7:Formulations containing same composition and higher viscosity grade-HPMC K 100M
N_1 – N_7: Formulations containing same composition and lower viscosity grade HPMC K 4 M

Table 6
Evaluation of physical properties of pellets

Batches	Angle of repose (θ°)*	Bulk density (gm/cm^3)*	Tap density (gm/cm^3)*	Carr's index (%)*	Hausner's ratio (H)*	Yield (%) *	% sphericity*
L_1	22.8	0.53	0.58	8.62	1.09	94.2	94
L_4	24.78	0.57	0.64	10.9	1.12	93.2	92
L_7	26.2	0.59	0.68	13.2	1.15	90.0	85
M_1	23.2	0.52	0.57	9.7	1.1	95.1	93
M_4	24.2	0.54	0.61	11.5	1.12	93.4	92
M_7	26.3	0.56	0.65	13.8	1.16	91.2	88
N_1	22.0	0.51	0.57	10.5	1.11	94.6	92
N_4	22.5	0.52	0.59	11.8	1.13	91.8	90
N_7	25.0	0.56	0.64	12.5	1.14	91.5	85

**Standard deviation± n=3*

Table 7
Physical properties of pellets and type of flow

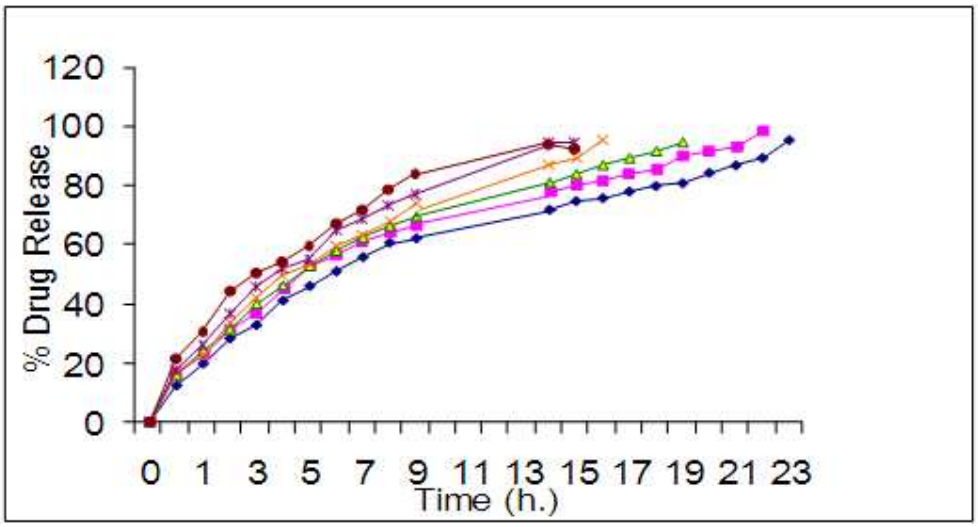
Angle of repose (θ°)	Carr's index (%)	Hausner's ratio (H)	Type of flow
>20	5-15	-	Excellent
20-30	12-16	<1.25	Good
30-40	18-21	-	Fair to Passable
-	23-35	>1.25	Poor
-	33-38	1.25-1.5	Very poor
>40	>40	-	Extremely poor

The controlled release Ranitidine tablets were further tested for *in vitro* drug release in pH 7.2 buffer. The data obtained for *in vitro* release were fitted into equations for the zero-order, first order and Higuchi- release models. Plots of % drug release versus time (zero order plot) and log % retained versus time (first order plot) were not found linear. However the plots of % drug release versus square root of time were linear (Table 8). The interpretation of the data was based on the value of the resulting regression coefficients. The *in vitro* drug release showed the highest regression coefficient values for the Higuchi's model indicating matrix diffusion controlled drug release from CR ranitidine tablets. As the HPMC K100M concentration was increased from L_1 to L_7, the release rates were found to decrease from 88 mg/h$^{1/2}$ to 63.8 mg/h$^{1/2}$ and release was retarded for longer period of time (Fig. 1). The $t_{50\%}$ and $t_{90\%}$ values increased gradually from 3.1 & 12.3 h for L_1 to 5.8 & 21.0 h for L_7 respectively. Percentage swell at 16 h time period showed gradual increase from 191% to 348.6 % with increase in polymer concentration.

Table 8
Release of ranitidine hydrochloride from selected tablet formulations

Tablet	$t_{10\%}$ h	$t_{50\%}$ h	$t_{90\%}$ h	Zero Order Release r value	First Order Release r value	Higuchi model r value
L_1	0.2	3.1	12.3	0.934	0.990	0.991
L_4	0.4	4.5	17.2	0.960	0.985	0.997
L_7	0.4	5.8	21.0	0.962	0.956	0.996
M_1	0.2	2.7	11.1	0.938	0.995	0.990
M_4	0.3	4.2	15.0	0.965	0.953	0.999
M_7	0.3	5.4	16.2	0.977	0.959	0.998
N_1	0.2	2.6	11.2	0.965	0.962	0.990
N_4	0.3	4.0	14.5	0.979	0.962	0.997
N_7	0.3	5.2	15.5	0.984	0.957	0.995

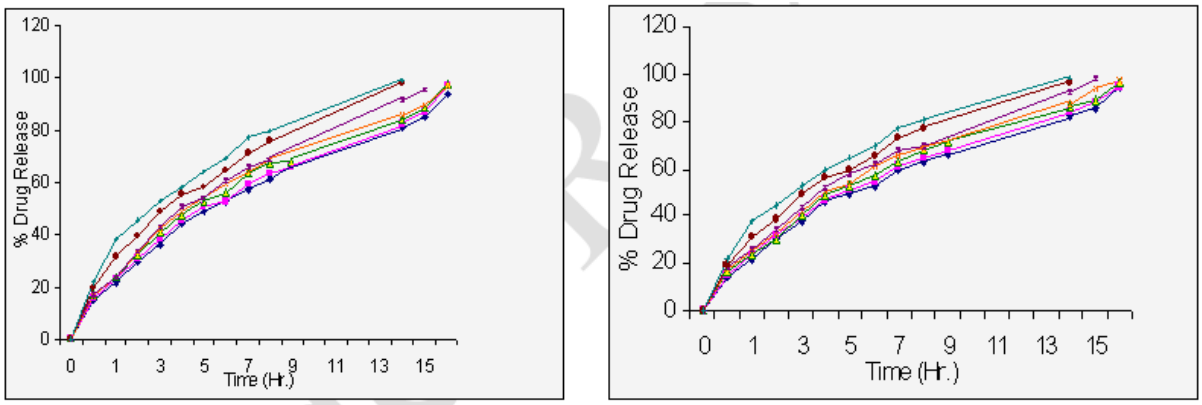
Figure 1
Dissolution profile of Ranitidine hydrochloride tablets, containing HPMC K 100M as rate controlling polymer



( ) : Tablet L_1containing drug : polymer ratio 3:1
( ): Tablet L_2containing drug : polymer ratio 3:1.5
( ): Tablet L_3containing drug : polymer ratio 3:2
( ): Tablet L_4 containing drug : polymer ratio 3:2.5
( ): Tablet L_5 containing drug : polymer ratio 3:3
( ): Tablet L_7containing drug : polymer ratio 3:4

Invitro dissolution studies of formulations M_1-M_7 and N_1-N_7 also showed matrix diffusion controlled drug release profiles. Dissolution rate was faster for M_1-M_7 containing HPMC K15M as compared to L_1-L_7. The release rate was reduced from 89 mg/$h^{1/2}$ to 72.88 mg/$h^{1/2}$ for M_1 to M_7 with increase in $t_{90\%}$ values from 11.1 h to 16.2 h (Fig. 2). The formulations N_1-N_7 showed still faster drug release. The release rates decreased gradually from 91.3 mg/$h^{½}$ to 75.2 mg/$h^{½}$ as proportion of HPMC K4M was increased. Thus in vitro drug release was found to vary among the formulations depending on the compositions and viscosity of polymers used. The dissolution data obtained indicates the matrix diffusion controlled drug release for all formulations. HPMC matrix pellets in a compressed form, delay the interaction of drug with dissolution medium by limiting the solvent penetration rate. Thus, in this system the burst effect is controlled and drug release is maintained relatively at constant level. Ranitidine release was retarded from the tablets as the proportion of HPMC was increased in pellets. The release rate was modulated by varying concentration of different viscosity grades of rate controlling polymer. HPMC is a well established hydrophilic polymer, has been extensively used in the design of sustained / controlled release delivery system[20,30,31]. The highly viscous polymer methocel™ used in composition, is mainly responsible for formation of swollen hydrated mass and controlled release of drug. The % swell values at 16 h time period were found to increase with increase in polymer concentration from 216.5 to 340.4% for M_1 to M_7 and from 200.5 to 328.8% for N_1 to N_7 respectively. Tablets containing higher viscosity grade HPMC, retarded the drug release for longer period of time and showed higher % swell values as compared to those containing lower viscosity grades.

Figure 2
Dissolution profile of Ranitidine hydrochloride tablets containing HPMC K 15M and HPMC K 4M as retardant.



Tablets (M) containing HPMC K 15M **Tablets (N) containing HPMC K 4M**

( ) : Tablet M_1 , N_1 formulation containing drug : polymer ratio 3:1
( ) : Tablet M_2 , N_2 formulation containing drug : polymer ratio 3:1.5
( ) : Tablet M_3 , N_3 formulation containing drug : polymer ratio 3:2
( ) : Tablet M_4, N_4 formulation containing drug : polymer ratio 3:2.5
( ) : Tablet M_5 , N_5 formulation containing drug : polymer ratio 3:3
( ) : Tablet M_6 , N_6 formulation containing drug : polymer ratio 3:3.5
( ) : Tablet M_7 , N_7 formulation containing drug : polymer ratio 3:4

Tablet formulation L_4 containing drug : polymer ratio of 3:2.5 had good micromeritic properties, % sphericity and desired drug release viz. 10 % drug released in 24 minutes, 50 % drug in about 4.5 h and 90 % drug in 17.5 h. Thus it showed a consistent and steady drug release profile with drug release rate of 66.3 mg / $h^{1/2}$ and can be used for once a day administration. Initially tablet has swollen at a faster rate with more than 150 % swelling in first hour and 200 % at the end of 4 h. This was followed by more steady swelling up to 24 h (Table 9). In early phase of dissolution, wetting of HPMC macromolecules at tablet surface occurs resulting in formation of gel layer, prominently visible after one hour. The release is controlled by penetration of dissolution medium through the gel layer and diffusion of drug through swollen hydrated matrix. As the external HPMC gel layer is depleted, wetting and swelling of inner layers of matrix constantly create new surface layer for drug diffusion, thus compensating for the increase in gel thickness and maintaining constant drug release for prolonged time period. The gradual swelling of a tablet to form a swollen hydrogel matrix was photographed at the end of 0, 4, 8 and 16 h time period during dissolution (Fig 3). The transverse section of swollen tablet at 8h time point was taken and photographed as shown in Fig 4, which further supports the mechanism of drug release and dissolution data. The photograph of T. S. at 8 h time period indicates that there is a distinct inner core at the centre of swollen tablet and part of total drug has been released from and through the outer gel layer of a tablet and remaining will be released subsequently from the inner core during dissolution.

Table 9
Percentage swell of selected tablet formulation (L_4) during dissolution study.

Time (h)	% Swell (n=3)
1	120.0
2	124.3
3	130.8
4	138.4
5	158.4
6	160.3
7	170.1
8	195.6
16	261.6

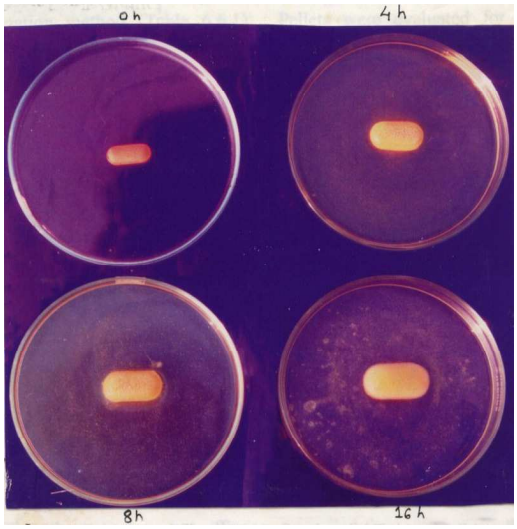


Figure 3
Photograph of tablet L_4 during in-vitro dissolution studies at 0 h, 4h, 8h and 16 h time period

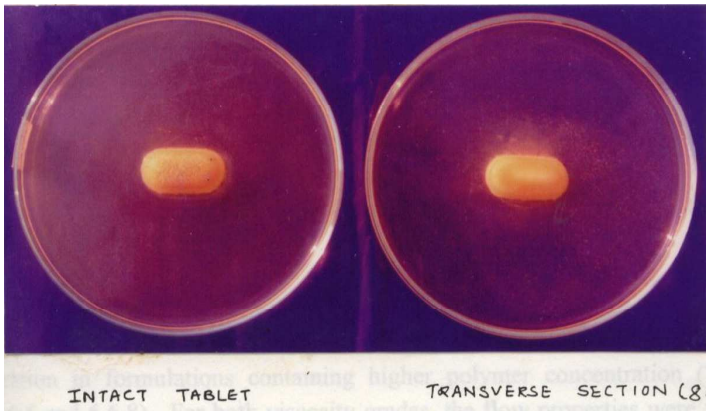


Figure 4
Transverse section of tablet L_4 during in-vitro dissolution studies at 8h time period.

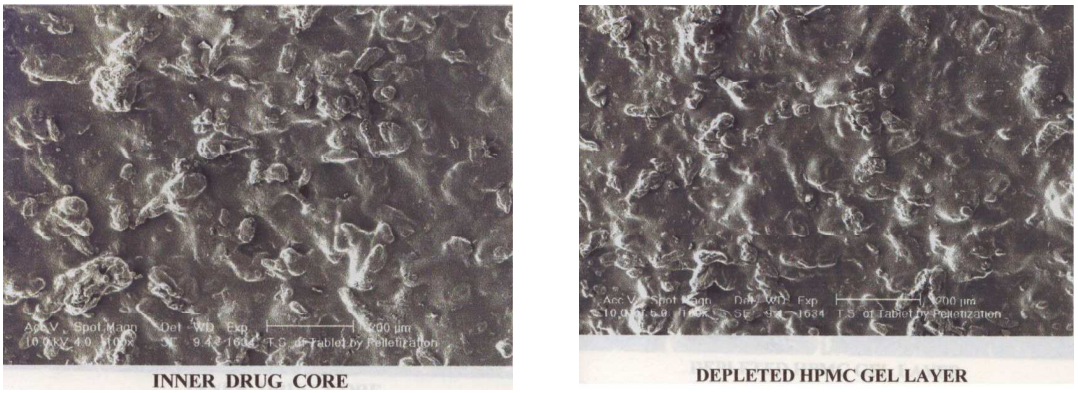


Figure 5
Scanning Electron Micrographs of T. S. of tablet L_4 at 8 h dissolution time period.

The transverse section of tablet L_4 at 8 h time interval of dissolution study was suitably processed for scanning electron microscopy. SEM photomicrographs (Fig 5) show inner core containing hydrated drug pellets and outer drug depleted gel layers of HPMC, thus illustrating diffusion through swollen hydrated matrix. It was predicted from dissolution study ex-vivo and photographs, that this swollen and expanded matrix system possesses the ability to control the gastric emptying time and it will be retained in the stomach for prolonged time to release the drug in a controlled manner. Release rate profiles in this study clearly demonstrated that linear kinetics can be easily achievable using HPMC/ MCC/ Lactose matrix pellets in compressed form. Tablet formulation L_4 which showed optimum drug release was film coated using ready to use coating mixture of Instacoat moistshield ICMS 251 obtained from IdealCures Ltd. (HPMC based non aqueous film coating). Film coated controlled release final tablet formulation L_4 was subjected for accelerated stability studies. Stability studies were carried out at 40° ±1°C and 75% ± 5% RH for a period of 90 days. The drug content study reveals uniform distribution of the drug in the tablets. It is also evident that L_4 exhibited good chemical stability under the investigated period (Table 10). In vivo evaluation and correlation with in vitro evaluation need to be carried out to assess efficiency and application of this system.

Table 10
Drug content and drug release from optimized tablet formulation L_4 during stability study

Sampling time in weeks	Drug Content* (%)	Drug Release Rate * (mg / h $^{1/2}$)
0	100.5	66.3
2	100.2	66.4
4	99.0	67.0
8	97.8	66.2
12	98.0	65.0

Standard deviation ± n=3

CONCLUSIONS

Controlled release swellable matrix tablets of Ranitidine hydrochloride were successfully formulated using extrusion-spheronization technique. Free flowing, hard and discrete pellets of drug were prepared after optimization of formulation and process variables, and further compressed into elegant tablets. The large single tablet undergoes significant swelling after oral administration, inhibits gastric emptying and

releases the drug continuously in predetermined and reproducible manner. Formulation L_4 , an ideal swellable controlled release matrix tablet formulation for once daily administration, provides a diffusion controlled, prolonged and consistent drug release up to 17 h at lower polymer concentrations (drug : polymer ratio of 3:2.5). Thus the release of ranitidine hydrochloride was sustained for >12 h compared with commercial conventional tablets which release the drug completely within 30 min. Good stability was observed for 3 months during stability studies. Thus it can be concluded that the prepared CR ranitidine hydrochloride tablets demonstrate the potential use of pellets of drug, MCC and release retardant HPMC K100 M for development of gastroretentive swelling matrix system, ultimately achieving desired steady state concentration and increased bioavailability of drug.

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