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Influence of barium sulfate X-ray imaging contrast material on properties of floating drug delivery tablets

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ABSTRACT

The objective of the study was to reveal the influence of necessarily added barium sulfate ($BaSO_4$) X-ray contrast material on floating drug delivery tablets. Based on literature survey, a chosen floating tablet composition was determined containing HPMC and carbopol 943P as matrix polymers. One-factor factorial design with five levels was created for evaluation of $BaSO_4$ (X_1) effects on experimental parameters of tablets including: floating lag time, total floating time, swelling-, erosion-, dissolution-, release kinetics parameters and X-ray detected volume changes of tablets. Applied concentrations of $BaSO_4$ were between 0 and 20.0% resulting in remarkable alteration of experimental parameters related especially to flotation. Drastic deterioration of floating lag time and total floating time could be observed above 15.0% $BaSO_4$. Furthermore, $BaSO_4$ showed to increase the integrity of tablet matrix by reducing eroding properties. A novel evaluation of dissolutions from floating drug delivery systems was introduced, which could assess the quantity of drug dissolved from dosage form in floating state. In the cases of tablets containing 20.0% $BaSO_4$, only the 40% of total API amount could be dissolved in floating state. *In vitro* fine resolution X-ray CT imagings were performed to study the volume change and the voxel distributions as a function of HU attenuations by histogram analysis of the images. X-ray detected relative volume change results did not show significant difference between samples. After 24 h, all tablets containing $BaSO_4$ could be segmented, which highlighted the fact that enough $BaSO_4$ remained in the tablets for their identification.

1. Introduction

Floating drug delivery systems (FDDSs) are classified in the group of gastroretentive drug delivery systems (GRDDSs) as having ability to float and be retained in the gastric medium for prolonged interval. Increased gastric retention of dosage forms allows local, stomach-specific - or sustained drug delivery aiming at long lasting effect *via* absorption. In order to evaluate and compare floating preparations, imaging techniques such as gamma scintigraphy, X-ray radiography, or more advanced X-ray computed tomography (CT) may be used to track *in vivo* floating and gastroretention (Arora et al., 2005). X-ray modalities are generally used imaging techniques for both clinical or research aims. X-ray CT instruments acquire planar X-ray projections around the patient or specimen, which are then reconstructed in order to gain spatial data of X-ray attenuation values in specific voxels (Wathen et al., 2013). The attenuation is generally expressed in Hounsfield units (HU).

X-ray imaging utilizes barium sulfate ($BaSO_4$) as a frequently applied positive X-ray contrast material (CM) for imaging or diagnostic purposes (*e.g.* imaging of the gastrointestinal tract) due to its proper mass attenuation coefficient. $BaSO_4$ is a white to yellowish powder having properties of inertness, opacity, high specific gravity and low solubility. It is only used orally or rectally. $BaSO_4$ is not absorbed or metabolized in physiological conditions and is excreted *via* feces in unchanged form (Widmark, 2007). $BaSO_4$ improves the visualization on X-ray images, as X-ray attenuation of $BaSO_4$ provides appropriate contrast in CT imaging.

In several published articles, $BaSO_4$ was utilized in the experiments in various amounts from 11.1 to 66.7% or the used amount of $BaSO_4$ was considered to be insignificant or to have minimal influence on floating properties of the tablets. In these articles, the dosage forms were broadly tested *in vitro* with an "original" composition and then the dosage forms with different compositions (part of the ingredients were replaced by certain amount of $BaSO_4$) were examined in *in vivo* X-ray studies. The possible changes in *in vitro* experimental parameters due to $BaSO_4$ addition were not extensively investigated.

Applied $BaSO_4$ in these articles is shown in Table 1.

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Table 1
Summary of $BaSO_4$ application in floating and non-floating drug delivery systems as X-ray CT contrast material.

Dosage form	$BaSO_4$ concentration	Total weight	Reference
A) Floating drug delivery systems			
Floating tablet	34.6% (90 mg)	260.0 mg	(Suresh et al., 2013)
Floating tablet	30.0% (150 mg)	499.5 mg	(Rao et al., 2013)
Floating mini-tablets-in-capsule	20.0% (140 mg)	700.0 mg	(El-Zahaby et al., 2014)
Floating tablet	19.4% (40 mg)	206.0 mg	(Srikanthn et al., 2012)
Floating tablet	15.4% (54 mg)	350.0 mg	(Baumgartner et al., 2000)
Floating tablet	14.8% (100 mg)	675.0 mg	(Guguloth et al., 2011)
Floating tablet	14.3% (100 mg)	700.0 mg	(Tadros, 2010)
Floating tablet	14.0% (42 mg)	300.0 mg	(Bomma and Veerabrahma, 2014)
Floating tablet	11.1% (20 mg)	180.0 mg	(Someshwar et al., 2011)
Floating tablet	10.0% (55.7 mg)	557.8 mg	(Dios et al., 2015)
Floating tablet	not mentioned	900.0 mg	(Reddy et al., 2012)
Floating tablet	not mentioned	500.0 mg	(Doodipala et al., 2011)
Floating tablet	not mentioned	500.0 mg	(Nama et al., 2008)
Floating tablet	not mentioned	200.0 mg	(Shah et al., 2010)
Floating tablet	not mentioned	250.0 mg	(Gnanaprakash et al., 2010)
B) Non-floating drug delivery systems			
Compression coated tablet for colon drug delivery	66.7% in core (100 mg)	600.0 mg (150.0 mg core)	(Momin and Pundarikakshudu, 2005)
Gastroretentive mucoadhesive tablet	62.5% (375 mg)	600.0 mg	(Sonani et al., 2010)
Matrix tablet for colon drug delivery	13.2% (100 mg)	760.0 mg	(Tugcu-Demiroz et al., 2004)

As previously mentioned, $BaSO_4$ has high specific gravity ($\rho = 4.5$ g/cm^3 (Perry, 2011)), which consequently increases the average density of the floating tablets likely influencing their floating parameters. Besides being practically insoluble, $BaSO_4$ powder has hydrophilic surface and can be wetted easily (Bala et al., 2006). Hence presence of inert insoluble particles entrapped in the matrix structure may also affect the wetting, swelling and/or erosion of tablets and thus drug release. The aim of these studies is to highlight the influences of $BaSO_4$, which have possibly significant role in manifestation of floating tablets.

In the present studies, commonly used excipients (HPMC and carbopol 943P) and quantities were based on published papers (Acharya et al., 2014; Charyulu et al., 2011; Kakad et al., 2012; Li et al., 2003; Narayana et al., 2013; Ranga et al., 2011; Spandana et al., 2013; Streubel et al., 2003) in order to examine a sustained-release floating tablet with well-known properties. Metoprolol succinate was chosen as model active pharmaceutical ingredient (API) due to its wide range application in floating systems. In these floating compositions, various amounts (0.0, 5.0, 10.0, 15.0, 20.0%) of $BaSO_4$ were added, and the influence of $BaSO_4$ on floating, swelling, eroding and drug release parameters was evaluated. X-ray CT images were captured and volume change of tablets was studied, furthermore histogram analysis was applied utilizing voxel number as a function of HU attenuation in order to reveal more difference between samples.

2. Materials and methods

2.1. Materials

Metoprolol succinate (PubChem CID: 62937) was used as active substance provided by Molar Chemicals, Hungary. Barium sulfate (Szkarabeusz Laboratory, Chemical and Commercial Limited Co, Hungary) was used as X-ray contrast material; hydroxypropyl methylcellulose and carbopol 934P were applied as matrix polymers. Viscosity grade of HPMC (2.0%) was measured to be 238.57 ± 24.07 mPa s and Carbopol 934P (0.5%) 7.96 ± 0.32 mPa s at constant 100 s^{-1} shear rate at 20 °C. Viscosity determination of solution was performed with the use of rotational viscometer (Anton Paar RheolabQC, Austria). Sodium bicarbonate (Hungaropharma, Hungary) was applied as effervescent agent. Talc, magnesium stearate and hydrophilic colloidal silica dioxide (Hungaropharma, Hungary) were used as excipients for tablet compression.

2.2. Methods

2.2.1. Experimental design, statistical analysis

One-factor factorial design was created to view the effects of $BaSO_4$ concentrations on experimental parameters. The composition matrix was consisted of one numeric factor. In the set-up, $BaSO_4$ (X_1) was examined in five levels (-1, -0.5, 0, $+0.5$, $+1$). The experimental layout is shown in Table 2. All tablets contained 100.0 mg metoprolol succinate and fixed concentration of tableting excipients contributing flotation of blends, and tablet compressing ability. Investigated dependent variables were the following: floating lag times (t_{lag}), total floating times ($t_{floating}$), swelling indices (S_i), tablet erosion (Remaining %), drug dissolution, parameters of release kinetics, floating specific dissolution % and relative tablet volume.

Data obtained from all floating tablet formulations were analyzed with Design Expert 7.0.0 software and used to generate the design and the response surface plots. Polynomial models were generated for all dependent variables including linear and quadratic terms with interactions. The best fitting models were selected based on statistical parameters including coefficient of variation (*CV*), coefficient of determination (R^2), adjusted and predicted coefficient of determination (adjusted and predicted R^2) provided by Design Expert software. Significant effects of factors on response, regression coefficients were determined using analysis of variance (ANOVA). *F*-test and *p*-values were also calculated and evaluated.

The following mathematical equation form was evaluated to determine numerically the effects of independent variables on particular

Table 2
Compositions of the effervescent floating tablet samples.

Samples	BF01	BF02	BF03	BF04	BF05
$BaSO_4$ (%)	0.00	5.00	10.00	15.00	20.00
Metoprolol succinate (%)	40.90	35.90	30.90	25.90	20.90
HPMC (%)	30.00	30.00	30.00	30.00	30.00
Carbopol 934P (%)	10.00	10.00	10.00	10.00	10.00
Sodium bicarbonate (%)	10.00	10.00	10.00	10.00	10.00
Mannitol (%)	5.00	5.00	5.00	5.00	5.00
Talc (%)	3.00	3.00	3.00	3.00	3.00
Magnesium stearate (%)	1.00	1.00	1.00	1.00	1.00
Colloidal anhydrous silica (%)	0.10	0.10	0.10	0.10	0.10
Total tablet weight (mg)	244.50	278.55	323.62	386.10	478.47