Influence of formulation technique on acrylate methacrylate copolymer modified paracetamol matrix tablets

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Abstract: This work was designed to evaluate the influence of various methods such as dry granulation (DG), wet granulation (using the polymer in an ethanolic solution (WGO) or aqueous dispersion (WGA) and solid dispersion (SD) techniques, on properties of paracetamol matrix tablets prepared using varying concentrations of acrylate methacrylate copolymer. Tablet properties were investigated using official and unofficial standards. Drug dissolution profile assessed at pH 1.2 was studied spectrophotometrically at λ_{max} of 245 nm. With the use of various kinetic models, the release mechanism of the drug was analyzed. The parameters, maximum amount of drug release (m_∞) at time t_∞ were obtained, m_∞ was ≥ 91.36 %, while t_∞ was ≥ 4.5 h. The release rate constant (k) for DG tablets was 15.61 h^{-1}, while, WGO, WGA and SD tablets were 12.90, 11.03 and 10.75 h^{-1} respectively. The matrix tablets, which exhibited marked retardation in drug release displayed a Higuchi square root of time model ($R^2 > 0.98$). The mechanism through which the drug was released was governed by Fickian diffusion release (n values < 0.5). The performance of the drug was affected by the formulation technique in the order of SD > WGO > WGA > DG.

Keywords: Matrix tablets, Paracetamol, formulation techniques, release kinetics, acrylate methacrylate copolymer, Higuchi, Fickian diffusion.

INTRODUCTION

Various approaches have been adopted over the years to develop and design pharmaceutical dosage forms that would meet desirable therapeutic benefits. Such techniques include the coating of solid particles and tablets with polymeric agents (Azarmi *et al.,* 2002), spheronization methods, modification of polymer chemistry and formation into matrix non-disintegrating systems using polymeric or hydrophobic lipoidal agents (Chithaluru *et al.,* 2011) as means of sustaining the release profiles of the drugs or bioactive agents. These techniques other than matrix methods are complex, tedious and they require the use of complex equipment for their formulations, which are not readily available. Other simpler approaches that have been adopted for the design of sustained release formulations present certain therapeutic failures and drawbacks such as dose dumping, over dose toxicity, undesired burst release or excessive delayed and/or excessive prolongation that would be harmful to the patient (Gupta and Robinson, 1992). Among the various techniques of formulation of sustained drug release tablets, non-disintegrating matrix appears as one of the most efficient and interesting because of its flexibility in terms of the range of release profile attainable, cost effectiveness and limited risk (Wadher *et al.,* 2011). Matrices are considered as the simplest system in the formulation of sustained release tablets (Bruce *et al.*, 2005). There has been little or no consideration given to the understanding of the principle underlining the release mechanism of drugs formulated using different mechanism. The need to have an increased understanding of these principles cannot be over emphasized. Hence, this work was designed to investigate the effect of various formulation techniques and polymer concentration on the properties of matrix formed with acrylate methacrylate copolymer using paracetamol as model drug and the underlying kinetics governing the release profiles.

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MATERIALS AND METHODS

Materials

Acrylate methacrylate copolymer was a gift from Rohm Pharma (GmBH, Darmstadt, Germany) was the polymer used in this study as a binder. Paracetamol powder was obtained from Nomagbon Pharmaceutical Company, Benin City, Nigeria, and used as a drug model. Maize starch (disintegrant) and magnesium stearate (lubricant) were obtained from BDH Chemicals, (UK). All the other chemicals and reagents used were of analytical grade.

Methods

Granule preparation

Four different techniques were used to prepare the granules as follows:

Dry granulation

Paracetamol powder (50 g) was mixed thoroughly with varying proportions of the polymer (0-10% w/w) based on the weight of the active drug. The powdered mix was slugged using a single punch-tableting machine (Manesty Machines Ltd., UK) at compression load of 40 arbitrary unit. The slugs (large tablets) produced were reduced into

granules and screened using an Endecotts sieve (model: BS 440, England) of 850 µm aperture size (Thapa *et al.,* 2005). The granules were placed in a desiccator for 24 h prior to characterization and tableting.

Wet granulation (using organic and/or aqueous dispersion)

Paracetamol powder (50 g each) was wet massed with sufficient quantity of either organic solution or aqueous dispersion of the polymer (0-10% w/w) formed by a procedure described previously by Eichie *et al.,* 2008, to form a crumbly mass. Granules were formed by passing the mass through an 850µm aperture size sieve and they were dried for 4h in a Morgan and Grundy hot air oven at 60°C. The dried granules were placed in a desiccator for 24 h before evaluation and tableting.

Solid dispersion

Paracetamol powder (50 g) and varying proportions of the polymer (0-10% w/w) were mixed and dispersed in 300ml of ethanol overnight with occasional stirring to form a homogeneous dispersion (Swain *et al.,* 2011). The dispersion was then evaporated to dryness at 60ºC for 1 h. After drying the mass was screened with the use of an 850 µm aperture size sieve.

Conventional granulation

This was prepared by blending sufficient quantity of 15% w/v starch mucilage with 50g of paracetamol powder. The resulting mass was initially screened with the use of a 1.7 mm aperture size sieve and oven dried for 1 h. The semi-dried granules were again screened using an 850 µm aperture size sieved, dried further at the same temperature for 4 h to obtain dry granules.

Evaluation of the granules

The bulk and flow properties of the granules such as bulk and tapped densities, and angle of repose were determined using standard procedures (Okoye *et al.,* 2012; Onyekweli, 2000). Carr's compressibility index (CI) was computed with the values obtained.

Preparation and evaluation of tablets

Maize starch B.P. (5% w/w) was mixed thoroughly with each batch of the granules prior to tablet production. Granule weight equivalent to 500mg paracetamol were compressed into tablets using a single punch-tableting machine (Manesty machines, Type P3 No/5L 182, England) that had its load for compression placed at 30 arbitrary unit (AU). Prior to tableting, magnesium stearate (1% dispersion) was used to prevent sticking). Tablets were evaluated for, tensile strength (T) and friability (%) were determined following standard procedure (Fell and Newton, 1970; USP, 2004)

In vitro dissolution studies

The USP type 1 method was used (USP, 2004). The medium for dissolution was 0.1 M hydrochloric acid (900 mL) and kept at 37±0.5ºC for 12 h. At specified time intervals, 5 mL samples were withdrawn. Equal amount of fresh dissolution medium was transferred into the dissolution vessel to replace the withdrawn sample. The withdrawn samples were filtered and their absorbance determined using a UV/visible spectrophotometer (PG instruments T70, USA) at λ_{max} 245 nm. Triplicate determinations were made and mean values were reported with their standard deviations.

Kinetics of drug release

In ascertaining the kinetics and mechanism through which the drug was released the data obtained from dissolution were evaluated with the use of different kinetic models, such as Zero (eqn. 1) and First order (eqn. 2), and Higuchi (eqn. 3) models respectively, as shown below (Eichie and Okor, 2002; Dash *et al.,* 2010).

$m = k_o t$ …. (1)

$log\ m_1 = log\ m_o - 0.43 k_1 t$ …. (2)

$m = k_H\ t^{0.5}$ …. (3)

Where m = amount of drug released at time, t; m_1 = residual drug amount; m_0 = initial amount of drug; k_0, k_1, k_H and k=release rate constants for the zero, first, Higuchi and Korsmeyer models, respectively.

The drug release was considered to be in accordance with a kinetic order if the correlation coefficient was ≥0.95 (Eichie *et al.,* 2005). The data obtained from dissolution were also analyzed using Korsmeyer model (eqn. 4) (Korsmeyer, 1983).

$m/m_o = kt^n$ …. (4)

The magnitude of n, which is the release diffusion exponent, indicates the mechanism through which the drug is released. For n being ≤0.5 means Fickian diffusion release, >0.5 and <1.0, indicates an anomalous behavior and for n equals 1 implies zero order.

RESULTS

All granules displayed angle of repose ranging from 31.05 -36.84º and Carr's Index ranging from 10.62-14.52% respectively (table 1). There was slight decrease in these values as polymer concentration increased. However, these decreases were not significant (P>0.05).

All tablets displayed low friability values of ≤0.89% with the exception of those formed with polymer concentration ≤5% w/w by dry granulation technique, which displayed friability values ranging from 1.1 to 6.42% (table 1). These same tablets also exhibited low tensile strength ranging from 0.49-0.87, which was considered

Table 1: Effect of formulation technique and polymer concentration on the properties of granules and tablets

Formulation technique	Polymer concentration (% w/w)	Angle of Repose (π) (mean ± SD)	Carr's compressibility index (%) (mean ± SD)	Friability (%) (mean ± SD)	Tensile strength (MNm^{-2}) (mean ± SD)
Conventional	0	32.14±0.82	10.91±0.71	0.85±0.04	0.80
Dry granulation	1	36.84±0.71	14.52±0.32	6.42±0.02	0.49
	3	36.51±0.52	14.14±0.81	4.35±0.01	0.61
	5	35.60±0.39	14.10±0.62	1.10±0.07	0.80
	10	34.03±0.76	12.66±0.75	0.75±0.05	0.81
Wet granulation (organic solvent)	1	34.01±0.37	12.72±0.45	0.82±0.02	0.73
	3	33.22±0.62	12.07±0.37	0.68±0.04	1.10
	5	32.79±1.21	11.37±1.59	0.57±0.05	1.16
	10	32.05±0.41	11.10±0.69	0.49±0.05	1.19
Wet granulation (aqueous dispersion)	1	34.59±0.46	13.11±0.62	0.89±0.03	0.79
	3	34.16±0.55	12.70±0.89	0.61±0.05	1.10
	5	33.63±0.44	11.76±1.16	0.54±0.06	1.15
	10	32.86±0.61	11.29±0.69	0.37±0.08	1.35
Solid dispersion	1	35.02±0.21	12.96±0.71	0.84±0.04	0.72
	3	34.83±0.58	12.50±0.53	0.66±0.03	1.10
	5	34.46±0.71	11.78±0.46	0.50±0.05	1.15
	10	33.74±0.36	11.48±0.50	0.45±0.08	1.20

Table 2: The effects of polymer concentration and formulation technique on release parameters of paracetamolmatrix tablets

Polymer concentration (% w/w)	Release parameters											
	M_∞ (%)				T_∞ (h)				K (h^{-1})			
	DG	WGA	WGO	SD	DG	WGA	WGO	SD	DG	WGA	WGO	SD
1	91.36	92.67	91.39	91.47	4.5	5	5.5	6	19.12	16.73	15.21	14.74
3	91.68	92.53	91.56	91.48	5	6	6	6.5	18.49	15.44	14.71	14.27
5	91.59	92.4	93.53	93.02	6	7.5	8	8.5	15.61	12.90	11.03	10.75
10	90.77	93.42	92.11	92.58	7.5	8.5	10	10.5	12.25	10.96	9.50	9.83

significantly different (P>0.05) compared to the other techniques. At 10% w/w polymer concentration, tablets formed by the other techniques (WG and SD) had tensile strength values ≥ 1.19 MNm^{-2}. Generally, at low polymer concentration (1% w/w), the tensile strength of all tablets were remarkably low with value ≤0.79 MNm^{-2} and were closely related to the conventional tablet.

In vitro drug release

The parameters, maximum drug amount released (m_∞) attained at time (t_∞) are displayed in table 2. Values of the release rate constant (k) for DG tablets was 15.61 h^{-1}, the values for WGO, WGA and SD tablets were 12.90, 11.03 and 10.75 h^{-1}, respectively. Thus showing solid dispersion technique had the most influence on the retardation of the release of the drug out of the matrix system.

Release kinetics of the matrix tablets

In analyzing the linear regression of the dissolution data of the different kinetic models it was revealed that the release of the drug from the matrix had best linearity with the Higuchi kinetic model (R^2≥0.98). All the tablets produced demonstrated a distinct trend of drug release by Fickian diffusion, having n values <0.5, irrespective of the technique employed in their production (table 3).

DISCUSSION

Good flow characteristic is a desirable quality of solid dosage form (Barabasi *et al.,* 1999). All the granules displayed good flow properties and high degree of packing. Granules that are not free flowing can create bridges in the hopper during tableting leading to uneven filling of the die. Determination of flow characteristic serves as a useful tool for the uniformity of weights and content. Also, all tablets met the United States Pharmacopoeia (USP, 2004) specification of friability <1%, with the exception of tablets produced by dry granulation (≤5% w/w). This may either be attributed to lower cohesive exhibited due to the absence of fluid during the granulation process or inadequacy of the polymer in the granules especially among the smaller granule sizes, which could not impart enough degree of plasticity on granules. Tablet friability decreased as the

Table 3: Release kinetics of the different formulations based on the different release models tested

Formulation technique	Polymer concentration (% w/w)	Zero order	First order	Higuchi	Korsmeyer
		R^2	R^2	R^2	R^2 (n)
Conventional	0	0.1010	0.9692	0.7831	0.7597 (0.3242)
Dry granulation	1	0.6976	0.9746	0.9910	0.9861 (0.4354)
	3	0.7753	0.9683	0.9908	0.9877 (0.4202)
	5	0.8689	0.9177	0.9837	0.9750 (0.4508)
	10	0.8994	0.8919	0.9861	0.9423 (0.4860)
Wet granulation (organic solvent)	1	0.8230	0.9738	0.9872	0.9823 (0.4259)
	3	0.9019	0.9443	0.9879	0.9856 (0.4873)
	5	0.8742	0.9702	0.9916	0.9803 (0.4690)
	10	0.8934	0.8970	0.9905	0.9447 (0.4340)
Wet granulation (aqueous dispersion)	1	0.7435	0.9528	0.9877	0.9778 (0.4181)
	3	0.8999	0.9523	0.982	0.9767 (0.4744)
	5	0.8943	0.9244	0.9925	0.9551 (0.4350)
	10	0.8282	0.8718	0.9914	0.93739(0.4720)
Solid dispersion	1	0.8827	0.9165	0.9865	0.9837 (0.4728)
	3	0.8957	0.9462	0.9767	0.9692 (0.4886)
	5	0.9208	0.9676	0.9935	0.9818 (0.4750)
	10	0.9209	0.8767	0.9843	0.9756 (0.4780)

polymer concentration incorporated during formulation was increased. Tablet tensile strength is a measure of tablet mechanical strength and is characteristic of internal friction or cohesion of the particles. The low values of tensile strength exhibited by tablets formulated by dry granulation technique may be attributed to the absence of fluid in the binding agent. The tensile strength which was more marked with the other techniques may be because the polymer solution is known to gel and form a visco-elastic polymeric network during the drying process of the granules and this may have led to the formation of stronger interparticulate bond between the resulting granules during compaction (Lehman, 1968).

Tablets produced with polymer had a more prolonged release of the drug when compared with the conventional tablets. While the conventional tablets released 80% of their payload at 30 min, the matrix tablets released about 80% of their content at ≥3.5 h. The retardation in the release profile was concentration dependent. An increase in concentration of polymer induced a growth diffusion path length between the polymeric chains in the matrix system. Dry granulation technique had the least effect on the retardation of drug release as displayed by the release rate constant (k). This has shown that solid dispersion technique had the most influence on the retardation of the release of the drug from the matrix system.

All the tablets, irrespective of formulation technique had the best correlation with Higuchi model. The drug release from the polymeric tablets displayed a diffusion controlled mechanism. This was confirmed from the value of the release exponent (n) in Korsmeyer's equation having n<0.5. Hydrophobic polymers have also been reported to release the drug from their polymeric matrix by diffusion mechanism (Darunkaisorn and Phaechamud, 2011). In such a diffusion-controlled model, the systems are usually characterized by an initial zone of depletion, i.e. the surface layers are depleted of their drug content due to rapid leaching into the dissolution medium (Eichie *et al.,* 2008), thereby constituting a diffusion layer. It was also reported that the increase in time taken for the drug to be released is due to the fact that the depletion zone recedes inwards thereby causing an increase in the diffusion path length (Eichie *et al.,* 2008). Kinetic release from all the polymeric matrices was not affected by the type of formulation technique employed in the study.

Of all techniques employed, solid dispersion technique was the most effective. Although a sustained release was displayed by all tablets at 1% polymer concentration, dry granulation technique could not produce tablets hard enough to withstand mechanical shock at this concentration. In wet granulation technique, formulation of the granules had a longer processing time. The use of solid dispersion technique had the least processing time and produced tablets hard enough to withstand mechanical shock. Also this technique will be more economical in large-scale production because the organic solvent used (ethanol) can be recycled.

CONCLUSION

The incorporation of acrylate methacrylate copolymer resulted in the production of paracetamol matrix tablets irrespective of the technique employed in formulation. Tablet properties were influenced by the techniques used. Tablets formulated using dry granulation techniques were

more friable with less tensile strength when compared with the other techniques. Solid dispersion technique produced paracetamol matrix tablet that displayed the highest level of sustained release. Hence this technique can be applied when metacrylic acids and their derivatives as well as related polymers are applied in matrix drug formulation for sustained release.

ACKNOWLEDGEMENT

The authors are grateful to Rohm Pharma GmBH & Co. (Germany), for the gift sample of acrylate methacrylate copolymer used in the study.

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