RESEARCH ARTICLE

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Bisoprolol Hemifumarate Matrix Tablets for Sustained Release: Preparation and Evaluation

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Abstract: Bisoprolol hemifumarate is a selective beta-1-blocker used in the treatment of coronary heart failure. It is characterized by being freely water soluble. Very limited trials were developed to prepare sustained release dosage forms of this drug. In this work, it was possible to formulate it as matrix tablets containing 20 mg of the drug so as to extend its release over a period of more than five hours. Two groups of polymers were used: hydrophilic matrices including carboxymethyl cellulose and carbopol 974 and lipid matrices including stearyl alcohol and carnauba wax. These matrices were prepared at the following drug: polymer ratios 1:1, 1:3 and 1:4. Prepared tablets were examined for their hardness, friability, drug content and percentage of drug released. Stearyl alcohol used at a ratio of 1:4 brought about a percentage of drug released of 57.18% (±3.7) after 5 h and tablets exhibited zero order release rate. Carbopol at 1:4 ratio showed a zero order release with 73.52% (±8.7) of the drug released after 5 h.

INTRODUCTION

Oral route represents the oldest route for drug administration due to low costs and convenience of administration to patient. [1] Tablets constitute the most commonly used oral dosage forms. [2] The sustained release drug delivery devices that are administered orally allow maintenance of blood levels of the drug for a prolonged period of time. This helps to improve the compliance of the patient. [3]

Preparation of matrix tablets represents a popular way for preparing controlled release drug delivery systems. [4] Matrix tablets can possibly be prepared by dispersing the drug with hydrophilic [5] or hydrophobic matrices [6] which delay the drug release. Drug release occurs from such matrices by dissolving, diffusion [7] or erosion. [8]

A number of polymers are used to prepare matrix tablets. These include hydrogels, soluble polymers, biodegradable polymers, non-biodegradable polymers, mucoadhesive polymers and natural gums. [9] Such used polymers result in the formation of swellable controlled release systems of hydrophilic polymers [10] or diffusion of dissolved drug through channels in a hydrophobic polymer. [11]

Among hydrophilic polymers are methyl cellulose, carboxymethyl cellulose (CMC) and carbopol. Other hydrophobic polymers include waxes as carnauba wax and stearyl alcohol. Matrix tablets can be prepared by direct compression, [12] wet granulation [13] and by injection moulding. [14]

Bisoprolol hemifumarate is 1-(4-(2-isopropoxyethoxymethyl (phenoxy) -N-isopropyl-3-aminopropan-2-ol fumarate. It is a cardioselective β-blocker used in control of hypertension and angina pectoris. [15, 16]

It is available as immediate release tablets and its bioavailability is about 90%. However, a constant blood level of the drug requires multiple dosing. [17] Thus, it is better to formulate it as a controlled release dosage form that helps stabilize drug blood levels and reduce dosing frequency.

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MATERIALS AND METHODS

Bisoprolol hemifumarate, supplied as a gift from Global Napi Pharmaceutical Co., Egypt. Stearyl Alcohol was obtained from Merck, Germany. Carbopol 974, Carnauba Wax, Carboxymethyl Cellulose (CMC), Talc and Starch were obtained from Alnasr Chemical and Pharmaceutical Co., Egypt.

Preparation of Bisoprolol Hemifumarate Matrix Tablets

A number of formulations of matrix tablets were prepared containing 20 mg of bisoprolol hemifumarate. [18] Two categories of matrix forming polymers were used, namely, hydrophilic matrix (carbopol 974 and carboxymethyl cellulose) [19] and lipid matrix (carnauba wax and stearyl alcohol). [20]

The drug was combined with these polymers at three ratios of 1:1, 1:3 and 1:4 (drug: polymer) to obtain 12 formulations. Starch was used with low polymer ratio tablets to increase bulk and talc was used a lubricant at 5% [21] so as to facilitate the compression process. The composition of the formulations is given in Table 1.

Determination of the Flowability of Powdered Formulations

The angle of repose (Θ) and Carr's index (Ci) were determined for every formulation, according to the following equations:

$$\text{Tan } \Theta = 2h/d,$$

Where, d: Average diameter of the formed cone; h: height of the cone. [22]

$$\text{Carr's Index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100. \quad [23]$$

Compression into Tablets

The formulations with appropriate flow properties were directly compressed into tablets using a single punch machine (Tablet single punch press machine (Royal Artist, Bombay, India).

Evaluation of Bisoprolol Matrix Tablets

The successful tablet formulations were evaluated, by determination of tablet hardness (Tablet hardness tester,

Table 1: Bisoprolol Hemifumarate Matrix Tablet Formulations

Formulation	Polymer	Drug:Polymer	Starch (mg)	Final Tablet Weight (mg)
1		1:1	55	100
2	Carbopol 974	1:3	13.68	100
3		1:4	-	106
4		1:1	55	100
5	CMC	1:3	13.68	100
6		1:4	-	106
7		1:1	55	100
8	Stearyl alcohol	1:3	13.68	100
9		1:4	-	106
10		1:1	55	100
11	Carnauba wax	1:3	13.68	100
12		1:4	-	106

All formulations contained 5% by weight talc

Table 2: Flow Properties of the Different Powdered Formulations

Formulation	Angle of Repose Θ°	Carr's Index
1	31.47 (± 0.46)	45.23% (± 0.31)
2	41.08 (± 2.47)	52.62 (± 0.42)
3	37.35 (± 0.35)	43.94 (± 0.08)
4	44.61 (± 0.68)	42.05 (± 0.08)
5	34.72 (± 1.19)	40 (± 1.41)
6	32.98 (± 0.71)	40.5 (± 0.73)
7	29.64 (± 0.37)	35.78 (± 0.31)
8	36.87 (± 0.54)	42.93 (± 0.1)
9	37.54 (± 1.02)	42 (± 0.5)
10	43.45 (0.53)	45.5 (± 1.2)
11	40.61 (±0.81)	30.31 (±0.97)
12	37.1 (±0.4)	28.79 (±0.3)

The values in the table are the average of three experiments (±SD)

model TH3/500, Copley Scientific, Nottingham, UK), friability (Tablet Friability test apparatus, model FR1000, Copley Scientific Nottingham, UK) and weight variation. [24] Drug content was determined by sonication of crushed tablet in 50 ml of distilled water for one hour, followed by filtration. An aliquot of the filtrate was withdrawn, appropriately diluted with distilled water and the concentration of the drug was determined spectrophotometrically at λ_{max} 223 nm, [25] based on the built calibration curve.

The dissolution profile of the tablets was determined using the USP dissolution apparatus II (paddle method). The release medium was 900 ml of distilled water. The apparatus was run at 75 rpm and samples of 5 ml were withdrawn at determined time intervals and compensated for by distilled water. [26] The release was compared to that of the marketed formulation Concor® 10 mg. All experiments were conducted in triplets. The release order of the drug from the different formulations was calculated using Microsoft Excel 2010.

SEM

The shape and surface morphology of the best matrix tablet formulation was studied by using scanning electron microscope (Quanta FEG 250, USA). Both the dry tablet and a tablet previously immersed in water for a period of 3 h were mounted directly onto the SEM sample stub using double-sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 mmHg).

Statistical analysis:

The obtained results were statistically analysed using one way ANOVA at $P<0.05$ using SPSS 16 software (2007).

RESULTS AND DISCUSSION

Table 2 shows the calculated values of both the angle of repose Θ as well as the Carr's index for the different formulations. A high value of Carr's index indicated poor flow, thus all powdered formulations showed comparable flow. [27] From angle of repose, F7 possessed the best flow properties. F1, F5 and F6 possessed good flow properties. F3, F8, F9 and F12 showed fair flow. F2, F4, F10 and F11 showed passable flow. [28]

Being close in their flow properties, the powders were compressed into tablets. The different properties of the prepared formulations are recorded in Table 3. All matrix tablet formulations showed uniform weights.

Upon examining Table 3, it was clear that formulations containing CMC (formulations 4-6) showed unacceptable friability (>1%), as well as low hardness. The hardness was lowered by raising the amount of CMC which agreed with results previously reported in the literature. [29]. CMC has low extent of cross linking and gelling character that provided lesser extent of mechanical strength. [28, 29] Hence, formulations 4-6 were excluded from further investigation.

Table 3: Properties of Bisoprolol Hemifumarate Matrix Tablet Formulations

Formulation	Hardness (N)	% Friability	%Drug Content
1	9.9 (± 0.14)	0.5	91.21 (± 1.4)
2	15.5 (± 2.12)	0.43	90.5 (± 1.2)
3	20.3 (± 0.21)	0.21	95.9 (± 2.5)
4	1.04 (± 0.27)		97.9 (± 4.22)
5	0.6 (± 0.04)	More than 1%	95.6 (± 1.7)
6	0.4 (± 0.05)		90.2 (± 4.04)
7	2.38 (± 0.54)	0.78	101.6 (± 5.4)
8	2.63 (± 0.47)	0.63	93.2 (± 1.02)
9	2.8 (± 0.2)	0.53	92.7 (± 1.3)
10	2.55 (± 0.47)	0.76	92.4 (± 8.45)
11	3.5 (± 0.62)	0.54	91.3 (± 9.53)
12	3.53 (± 0.06)	0.31	90.5 (± 3.69)

The values in the table are the average of three experiments (± SD)

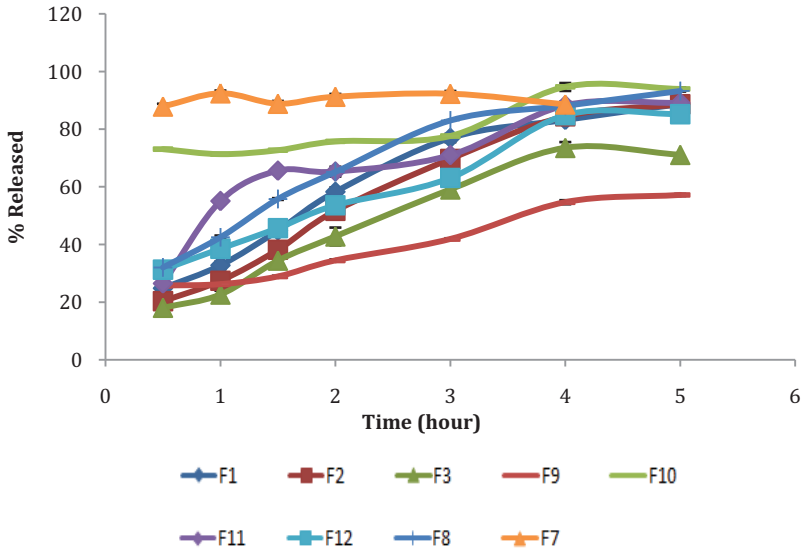

Figure 1: Dissolution pattern of bisoprolol hemifumarate matrix tablet formulations

Presence of Carbopol 974 increased the hardness values of the tablets. [30] Presence of Carbopol 974 in tablet formulations is associated by high compactibility. It shows high binding capacity which is reflected in high values for tablet hardness. [31]

All formulations showed acceptable drug content (90-105%). [28]

Figure 1 shows the dissolution pattern of the matrix tablet formulations. The percentage of drug released from matrix tablet formulations was compared to that released from the marketed product Concor® 10 mg, which showed 100% drug release within 10 minutes. The release order of the different formulations is given in Table 4.

It was evident from Figure 1, that matrix tablet F3 (containing 1:4 drug: carbopol) and matrix tablet F9 (containing 1:4 drug: stearyl alcohol) possessed relatively prolonged release rate, where the former released about 74% of the drug after 4 h and the latter released about 54% of the drug after 4 h. These two formulations showed zero order release rates. Comparing the rest of the formulations with each other concerning their release after 4 h, there was no significant difference at $P<0.05$.

Increasing the amount of Carbopol 974 in tablets resulted in reducing in the rate of release of drug. [32] Carbopol is a highly crossed linked polymer, resulting in formation of gel with high viscosity upon exposure to water. [33] The higher the viscosity is, the slower the release rate will be.

It was also observed that the higher the amount of stearyl alcohol, the slower the drug release. That was due to the lipid nature of stearyl alcohol, which repelled the water away from the drug, thus slowing down wetting and drug dissolution. [34] Hence, stearyl alcohol was more effective to reduce drug release compared to Carbopol. That was due to the hydrophilic nature of Carbopol, which, got hydrated. Despite gel production and increasing viscosity, Carbopol delivered water to drug, which was readily water soluble. That was unlike stearyl alcohol which sealed the drug away from water, hence, reducing its wettability and decreasing its release rate.

Concerning the tablet formulations prepared using carnauba-wax, they showed a release pattern comparable to the other formulations. It was expected to obtain a longer release period compared to stearyl alcohol, at the highest carnauba wax concentration (1: 4 ratio). However, higher release rates were obtained. That probably was due to the difference in melting points of carnauba wax compared to stearyl alcohol. Carnauba wax melted at 82°C,

Table 4: Release Order of Different Matrix Tablet Formulations

Formulation	Correlation coefficient R^2 Values			Release Order
	Zero	First	Higuchi	
1	0.9355	0.9904	0.9751	First
2	0.9655	0.9856	0.9827	First
3	0.9948	0.9824	0.9777	Zero
7	0.32	0.38	0.2	First
8	0.9245	0.9937	0.9764	First
9	0.9706	0.9626	0.931	Zero
10	0.8545	0.7962	0.7775	Zero
11	0.8554	0.9275	0.8897	First
12	0.9681	0.9374	0.9671	zero

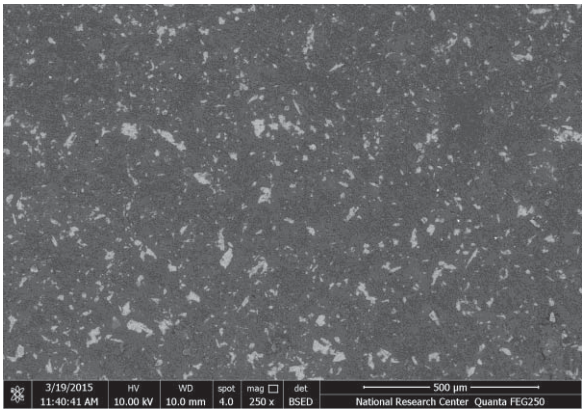

Figure 2: SEM of dry matrix tablet formulation F9

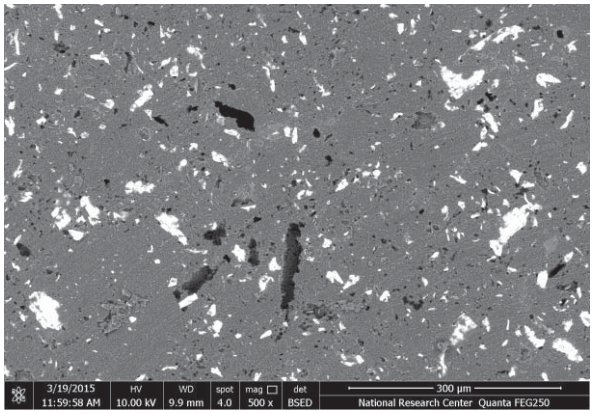

Figure 3: SEM of the wet matrix tablet formulation F9

whereas stearyl alcohol melted at 50°C. [21] This allowed stearyl alcohol to soften easily due to the heat generated upon tablet compression to form a covering layer at the tablet surface which allowed for a good coating of the drug with the hydrophobic stearyl alcohol layer and hence, insulating the drug from water. Carnauba wax, despite being more hydrophobic than stearyl alcohol, its melting point was higher than stearyl alcohol. It had no sufficient time during compression to soften and provide the water proof cover necessary to completely seal the drug away from water.

Examining the surface morphology of F9, consisting of 1:4 drug: stearyl alcohol ratio (which showed the longest release time), using SEM when dry and after immersion in water revealed the matrix tablet surface. Figure 2-3 showed the dry and wet tablet surfaces, respectively.

It is clear from Figure 2 that tablet surface is smooth. Upon immersion in water, pores appeared on the surface. That was due to solubility of the surface drug. Such formed pores were responsible for allowing the water to penetrate to inside the tablet. [35] Otherwise, the hydrophobic nature of stearyl alcohol could have retarded water penetration further to inside the tablet.

CONCLUSION

Hence it was concluded that, it is possible to prolong the release of the very soluble drug bisoprolol hemifumarate, through formulating it as matrix tablets using stearyl alcohol as a hydrophobic matrix at a ratio of 1:4 (drug: polymer).

REFERENCES

1. Sunil K A, Vaibhav G, Kuldeep M, Pankaj R. Oral extended release drug delivery system: A promising approach. Asian J Pharm Tech, 2:38-43, 2012.
2. Sharma A, Sharma S, Jha K K. The study of salbutamol matrix tablets using different polymers as release retarding agent. The PharmaRes,1:15-22, 2009.
3. Wang W, Yan H. Methotrexate-loaded porous polymeric adsorbents as oral sustained release formulations. Materials SciEng C, 78:598–602, 2017.
4. Varshosaz J, Tavakoli N, Kheirolahi F. Use of hydrophilic natural gums in formulation of sustained-release matrix tablets of tramadol hydrochloride. AAPS PharmSciTech, 7:E168-E174, 2006.
5. Krishnaiah Y S, Karthikeyan R S, Gouri Sankar V, Satyanarayana V. Three-layer guar gum matrix tablet formulations for oral controlled delivery of highly soluble trimetazidine dihydrochloride. J Control Release, 81:45-56, 2002.
6. Obaidat A A, Obaidat R M. Controlled release of tramadol hydrochloride from matrices prepared using glyceryl behenate. Eur J Pharm Biopharm, 52:231-5, 2001.
7. Maderuelo C, Zarzuelo A, Lanao J M. Critical factors in the release of drugs from sustained release hydrophilic matrices.J Control Release, 154:2-19, 2011.
8. Reza M S, Quadir M A, Haider S S. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J Pharm Pharm Sci, 6:282-91, 2003.
9. Dash T R, Verma P. Matrix tablets: An approach towards oral extended release drug delivery. Int J Pharma Res Rev, 2:12-24, 2013.
10. Abdel-Rahman S I, Mahrous G M, El-Badry M. Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets. Saudi Pharm J, 17:283-8, 2009.

11. Martini C M, Gravell K. Use of a hydrophobic matrix for the sustained release of a highly water soluble drug. Drug Dev Ind Pharm, 26:79-83, 2000.
12. Palem C R, Gannu R, Yamsani S K, Yamsani V V, Yamsani M R. Development of bioadhesive buccal tablets for felodipine and pioglitazone in combined dosage form: *in-vitro*, *ex-vivo* and *in - vivo* characterization. Drug Deliv, 18:344-52, 2011.
13. Barakat N S, Elbagory I M, Almurshedi A S. Controlled-release carbamazepine granules and tablets comprising lipophilic and hydrophilic matrix components. AAPS PharmSciTech, 9:1054-62, 2008.
14. Quinten T, Andrews G P, De Beer T, Saerens L, Bouquet W, Jones D S. Preparation and evaluation of sustained-release matrix tablets based on metoprolol and an acrylic carrier using injection moulding. AAPS PharmSciTech,13:1197-1211, 2012.
15. Schliep H J, Harting J. β_1-selectivity of bisoprolol, a new β-adrenoceptor antagonist, in anesthetized dogs and guinea pigs. J Cardiovasc Pharmacol, 6:1156-60,1984.
16. Dangat Y T, Bari N A, Swati C J, Chabukswar A R, Kuchekar B S. Controlled release from bisoprolol fumarate buccal patches. Der Pharmacia Sinca, 3:317-20, 2012.
17. Malakar J, Nayak A K, Goswami S. Use of response surface methodology in the formulation and optimization of bisoprolol fumarate matrix tablets for sustained drug release. ISRN Pharm [Internet]. Available from: https://www.hindawi.com/journals/isrn/2012/730624/.
18. Chatterjee S S. The cardioselective and hypotensive effects of bisoprolol in hypertensive asthmatics. Cardiovasc Pharmacol, 8(11):574-7, 1896.
19. Kiran S K, Rama T R, Jayaveera K N. Matrix tablets as controlled drug delivery systems. Indo Am J Pharm Research, 1:343-350, 2011.
20. Chandran S, Asghar L F A, Mantha N. Design and evaluation of ethyl cellulose based matrix tablets of ibuprofen with pH modulated release kinetics. Indian J Pharm Sci, 70:596-602, 2008.
21. Rowe R C, Sheskey P J, Quinn M E. Handbook of Pharmaceutical excipients, 7th Edition, Pharmaceutical Press, London, 700-1, 728-30, 2013.
22. Nazzal S, Nutan M, Palamakula A, Shah R, Zaghloul A A, Khan M A. Optimization of a self-nanoemulsified tablet dosage form of ubiquinone using response surface methodology: effect of formulation ingredients. Int J Pharm, 240:103-14, 2002.
23. Carr R L. Evaluating flow properties of solids. Chem Eng, 72:69-72, 1965.
24. European Pharmacopoeia. Vol 1. 9th ed. The directorate for the quality of medicines (EDQM), Pharmaeuropa Quarterly Forum Publication, Strasbourg, 3118, 2017.
25. Kakde V K, Barsagade A G, Chaudhary N K, Kale D L. Spectrophotometric method for simultaneous estimation of amlodipine besylate and bisoprolol fumarate in pharmaceutical preparations. Research J PharmTechn, 1:513-15, 2008.
26. Bisoprolol Fumarate Tablets. United States Pharmacopeia, 35/NF30, United States Pharmacopoeial Convention, Maryland, 2374- 2375, 2011.
27. Leon K J, Lieberman H A. The theory and practice of industrial pharmacy, 3rd edition, Varghese Publishing House, Bombay, 171-197, 1991.
28. Powder Flow. United States Pharmacopoeia, 35-NF30. The United States Pharmacopeal Convention, Maryland, 801-2, 2011.
29. Fiţa CA, Hîrjău V, Sala G, Karampelas O, Saramet G. The influence of formulation factors on the release of the metoprolol tartrate from extended release tablets. FARMACIA, 60:906-14, 2012.
30. Asaduzzaman, Elias-al-mamun, Saiful Islam, Jalil R. Effect of HPMC 4 Cps and Carbopol 974p NF on Release Kinetics of Ciprofloxacin From Kollidon® SR Embedded Matrix Tablets. J Pharm Sci Res, 1:137-45,2009
31. Aguilar-López Y A, Villafuerte-Robles L. Functional Performance of Chitosan/Carbopol 974P NF Matrices in Captopril Tablets. J Pharm 2016 (2016), Article ID 3240290, [cited 2017 Nov 5] Available from: http://dx.doi.org/10.1155/2016/3240290.
32. Khan G M, Jiabi Z. Formulation and *in-vitro* evaluation of ibuprofen-Carbopol 974P-NF controlled release matrix tablets. III: Influence of co-excipients on release rate of the drug. J Control Release, 54:185-90, 1998.
33. Bonacucina S M, Palmieri G F. Rheological, mucoadhesive and release properties of carbopol gels in hydrophilic cosolvents. Int J Pharm, 282:115-130,2004.
34. Adnan S, Ahmed S, Khan S M, Hassan S S. *In-vitro* comparison of sustained release hydroxypropylmethyl cellulose and lipid-based matrix systems of diltiazem HCl. Pakistan J Zoology, 42:515-19, 2010.
35. Abd El-Halim S M, Amin M M, El-Gazayerly O N, Abd El-Gawad N A. Comparative study on the different techniques for the preparation of sustained-release hydrophobic matrices of a highly water-soluble drug. Drug Discov Ther, 4:484-92, 2010.

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