FORMULATION AND CHARACTERIZATION OF MEDICATED CHEWING GUMS OF DEXTROMETHORPHAN HYDROBROMIDE

Swamy N.G.N.*, Shilpa P., Abbas Z.

(Received 01 June 2012) (Accepted 26 November 2012)

ABSTRACT

Chewing gums are mobile drug delivery systems, with a potential for administering drugs either for local action or for systemic absorption via buccal route. Dextromethorphan hydrobromide chewing gum formulations were made employing Pharmagum M as the base with an aim to overcome the first-pass effect, reducing the risk of overdosing, ease of administration and for achieving faster systemic absorption. Dextromethorphan hydrobromide was further transformed into spray dried form and incorporated into Pharmagum M base with the object of solubility enhancement and masking the bitter taste of the drug. The prepared medicated chewing gums were evaluated for various precompression and postcompression parameters. The *in vitro* drug release profiles were carried out employing Erweka DRT chewing apparatus. It was observed that increasing the chewing gum base concentration resulted in a decreased drug release profile. The drug in the spray dried form revealed improved performance in comparison to the directly contained drug. The drug release data were fitted into various kinetic models. It was observed that the drug release was matrix diffusion controlled and revealed a non-Fickian drug release mechanism. Accelerated stability studies were carried out on select formulations as per ICH guidelines. The formulations were found to be stable in respect to physical parameters and no significant deviations were seen in respect to *in vitro* drug release characteristics.

Keywords : Medicated Chewing gums, Dextromethorphan hydrobromide, Pharmagum M, Spray drying, Erweka DRT chewing apparatus

INTRODUCTION

Medicated chewing gums are solid, single-dose preparations that contain one or more active ingredients that are released by chewing[1]. This drug delivery system provides additional patient benefits and compliance, offering several advantages over tablets or liquid formulations in that, the therapeutic system is not be swallowed and this increases patient compliance, especially for geriatrics and pediatrics with swallowing disorders; moreover, the product can be taken anywhere and at any time as it does not require liquids to aid swallowing[2]. Chewing gum formulations have been evaluated for several drugs including aspirin[3, 4], verapamil[5], nicotine[6, 7], miconazole[8], nystatin[9], chlorhexidine gluconate[10], promethazine hydrochloride[11] and many more.

Most of the drug released from the gum through mastication is rapidly absorbed via the buccal cavity due to its large vascularization; therefore, a faster absorption results in a shorter duration of action. Alternatively, drug released from medicated chewing gum which is not absorbed through the oral cavity membranes will be swallowed and reach the stomach in a very fine dispersed form, thus being easily available for gastro-intestinal absorption with a consequent fast onset of action[12]. The oral mucosa is highly perfused with blood vessels having a blood flow of 20 – 30 ml/min for each 100g of tissue[13]. Drugs absorbed via the buccal cavity have direct access to the systemic circulation which bypasses intestinal and hepatic first-pass metabolism, thus potentially increasing their extent of absorption. Therefore it might be possible to administer a reduced dose in chewing gum in contrast to other oral drug delivery systems[14, 15].

*** For correspondence**
Department of Pharmaceutics
Government College of Pharmacy
Bangalore - 560027, Karnataka
E-mail : ngnswami@yahoo.co.in

The majority of chewing gum drug delivery systems are manufactured using conventional heating processes. As the heating process is involved, it may limit the application in case of thermally labile drugs; thus directly compressible, free flowing powdered gums could be used to replace the melted gum base. Pharmagum® base is a compressible gum system composed of a mixture of a polyol(s) and/or sugars with a gum base. These formulations can be compressed into a gum tablet using a conventional tablet press, enabling rapid and low-cost development of a gum delivery system[16].

Dextromethorphan hydrobromide (DXM) is an antitussive agent, used to relieve cough. DXM undergoes first-pass metabolism by oral route and exhibits only 11% oral bioavailability[17]. The present investigation was aimed at avoidance of first-pass metabolism of DXM by preparing medicated chewing gum, wherein drug is absorbed through buccal mucosa. Further, DXM is a drug with low water solubility and bitter taste[18, 19].

The aim of this study is to prepare immediate release DXM chewing gum by incorporating Spray dried DXM into the gum base to achieve enhanced solubility and to mask the bitter taste of the drug. In the present investigation, it is aimed to improve patient compliance, especially in patients with impaired swallowing abilities.

MATERIALS AND METHODS

Dextromethorphan hydrobromide and Pharmagum® M were provided as gift samples by Genovo Development Services limited, Bangalore and SPI Pharma limited, Bangalore respectively. Excipients such as Sucralose, Aerosil, Talc, Magnesium stearate, Mint flavour and Alizarin green colour were obtained as gift samples form Apotex Research Private Limited, Bangalore. All other reagents used were of analytical grade.

Procedure

Medicated chewing gums (MCG) were prepared using DXM and Pharmagum M in different drug to gum ratios. The MCG composition is presented in Table I. In formulations FS1, FS2, and FS3, DXM and other additives were spray dried and then incorporated into the Pharmagum M base. DXM chewing gums with conventional direct compression technique (FC2) were also prepared for comparison.

Preparation of MCG by spray dying process

DXM, sucralose and Aerosil were dispersed in 50 ml of ethanol by stirring (Remi stirrer, Mumbai) at 2000 rpm for 60s. The granules were obtained by spraying the feed solution with a spray drier (Mini Buchi B-191, Buchi laboratories, Flawil, Switzerland) using a standard 0.5mm nozzle. The DXM solution was fed to the nozzle with a peristaltic pump, atomized by the force of compressed air and blown together with heated air to the chamber where the solvent in the droplets were evaporated. The dried granules were harvested from the apparatus collector and kept under desiccator until further use. The operating conditions of the spray drying process were, an inlet temperature of 70 – 80^{0}C; an outlet temperature of 50 – 55^{0}C; spray pressure of about 2 atm and spray rate feed of 3 – 4 ml/min.

Mint flavor, Alizarin green colour and magnesium stearate were mixed and sifted through #60 ASTM, mixed throughly and kept aside. The spray dried granules were mixed with #40 ASTM sifted Pharmagum M and sorbitol. To this blend, the mixture of colour, flavor and magnesium stearate were added and mixed for additional 5 min. Finally to these granules, talc sifted through #60 ASTM was added and the granules were then subjected to compression to a target weight of 1000 mg using round shaped, flat faced, 12.00mm punches and dies.

Preparation of MCG by direct compression process

Mint flavor, Alizarin green colour, aerosil and magnesium stearate were mixed thoroughly, sifted through # 60 ASTM and kept aside. DXM and Pharmagum M were mixed with sorbitol and blended for 10 min. To the drug mixture, flavor, colour, aerosil and magnesium stearate were added and blended

for 5 min. To this talc was added and blended for 5 min and compressed as mentioned above.

Table I: Composition of chewing gum formulations (mg / tablet)

Composition	FS1	FS2	FS3	FC2
Dextromet-horphan HBr	10.00	10.00	10.00	10.00
Pharmagum M	800.00	850.00	900.00	850.00
Mint flavor	6.00	6.00	6.00	6.00
Aerosil	5.00	5.00	5.00	5.00
Sorbitol	136.00	86.00	36.00	86.00
Sucralose	15.00	15.00	15.00	15.00
Magnesium stearate	2.00	2.00	2.00	2.00
Talc	23.64	23.64	23.64	23.64
Alizarin green colour	2.36	2.36	2.36	2.36
	1000.00	1000.00	1000.00	1000.00

Characterization of the medicated chewing gums of DXM

Buccal Absorption Test

Buccal absorption test was carried out on 3 healthy human volunteers aged between 23 to 25 years[20]. The test consists of introducing 25 ml of drug solution prepared in simulated salivary fluid at a concentration of 1 mg/ml, at different pH values of 6.0, 6.5 and 7.0 in the oral cavity of the volunteers, who swirled it for 15 min and expelled out[21]. The expelled saliva was then diluted suitably and analyzed at 278 nm by UV spectroscopic method against the blank reagent. The composition of the simulated salivary fluid[22] is presented in Table II.

Determination of Pre-compression parameters

The formulated chewing gum granules were evaluated for Pre-compression parameters such as Bulk Density, tapped density, Carr's Index and Hausners ratio which are indicative parameters for flow and compressibility[23].

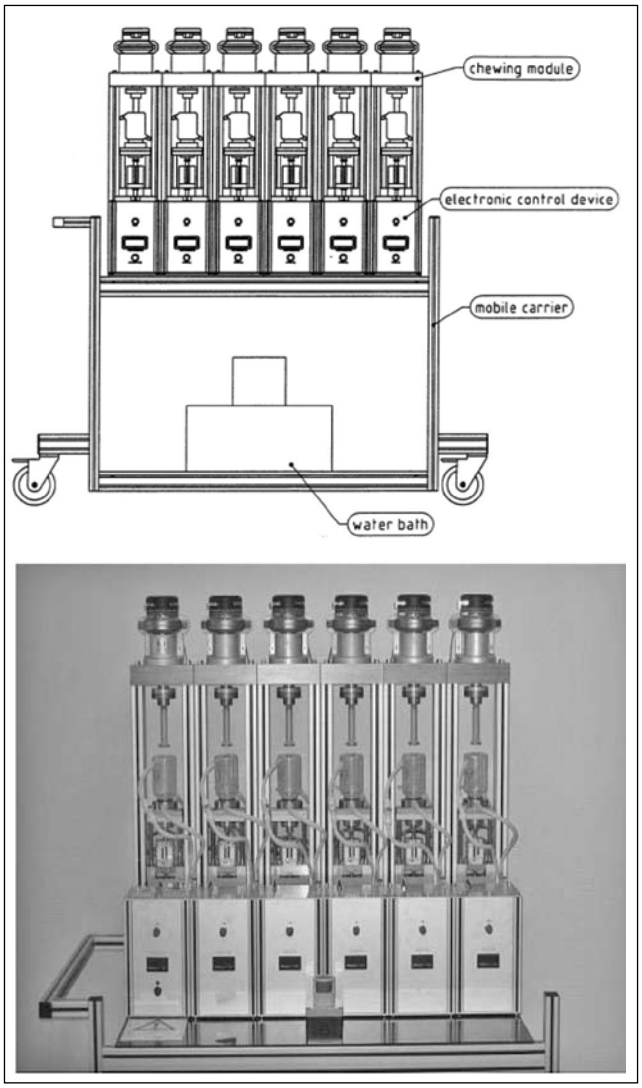

Fig. 1: Technical diagram and picture of Erweka's DRT 6 Chewing apparatus

Table II: Composition of simulated salivary fluid (SSF)

Composition	(g/L)
Potassium chloride	0.720
Calcium chloride dihydrate	0.220
Sodium chloride	0.600
Potassium phosphate monobasic	0.680
Sodium phosphate dibasic	0.886
Potassium bicarbonate	1.500
Potassium thiocyanate	0.060
Citric acid	0.030
pH	6.5

Determination of Post-compression parameters[24]

The formulated chewing gum tablets were subjected to weight variation test, tablet breaking force / hardness and friability determination.

Uniformity of Drug content: Ten units from each formulation were individually assayed for DXM content by crushing and dissolving each tablet in 100 ml of artificial salivary fluid. The solution was then filtered, suitably diluted and absorbance was read by UV spectroscopy at 278 nm[25]. The results are represented as mean drug content ± SD.

***In Vitro* drug release[26, 27]**

The *in vitro* drug release studies form the chewing gum formulation was performed using Erweka DRT chewing apparatus (shown in Fig. 1). The test cell of the apparatus was filled with 50ml of simulated salivary fluid (SSF) and the chewing gum was placed in the apparatus. The apparatus was operated at a chewing frequency of 56 strokes / min. 5ml of the SSF from the test cell was withdrawn at regular intervals of 5, 10, 15, 20, 25 and 30 min. 5ml of fresh SSF was replaced back in the test with each withdrawal of the sample. The volume withdrawn was made up to 25ml using SSF and absorbance of the resulting solution was read at 278.2nm.

***In Vitro* Drug release Kinetics**

For understanding the mechanism of drug release and release rate kinetics[28] of the drug from the dosage form, the obtained data was fitted into software (PCP – disso V2.08) with zero order, first order, Higuchi matrix, Krosmeyer & Peppas model by analyzing the R values, the best fit model was selected.

Stability studies

Accelerated stability studies[29] of the selected formulations were carried out as per ICH Q1A (R2). The select formulations were stored at $40^0 \pm 2^0$C/75% ± 5% RH for 3 months and evaluated for physical deformities and dissolution testing.

RESULTS AND DISCUSSION

In the present study, an attempt was made to formulate chewing gum of DXM using spray dried granules in order to mask the bitter taste and enhance the solubility of the drug substance. The aim of the formulation was to avoid first-pass metabolism and to improve the oral bioavailability.

Two different processes were evaluated to obtain MCG of DXM, the first process was spray drying which masks any unpleasant taste of the medicament and improve the solubility, followed by compression. In order to understand the benefits of spray drying process, a formulation was prepared by direct compression process which was used as a reference product.

Pharmagum M consists primarily of gum base and sorbitol. Three different formulations with different gum base concentration of 80%, 85% and 90% were prepared. Below 80% of the gum base, no gummy mass with good chewing characteristics was produced, while with 90% of the gum base, a bulk chewing mass was formed, thereby decreasing patient compliance as well as affecting DXM release from the prepared MCG. Sweeteners and flavours were used to obtain a fine pleasant taste. Co-adjuvant excipients like Aerosil, talc and magnesium stearate were added to the mixture to optimize the compression process and for anti-adherent properties.

Buccal absorption test showed that 79.6% of the drug is buccally absorbed within 15 min when available to the buccal mucosa at pH 6.0. Upon increase in pH to 6.5 and to 7.0 the % drug absorbed decreased from 75.2 to 73.6%

The physical parameters of the granules for all the formulated batches exhibited good flow which is indicated by the bulk and tapped density in the range of 0.470 g/mL to 0.550 g/mL and 0.520 g/mL to 0.590 g/mL respectively. The Carr's index was found to be in the range of 5.263% to 9.615% and Hausner's ratio was in the range of 1.056 -1.106, which is found to be acceptable.

The mean weight of 20 chewing gum tablets from each formula was determined. None of the tablets deviated by more than 5% from the mean weight, indicating that all the formulae fulfilled the pharmacopeial limits for weight variation. The mean percentage of DXM content in the chewing gum from each formulae were found to be in the range of 98.2 ± 1.80% to 99.2 ± 0.35%. The hardness of the compressed chewing gum formulation was found to be in range of 9.5 to 11.5 Kg/cm^2. All the formulae were found to conform to pharmacopeial limits of the label claim.

The release profile of DXM from the chewing gum tablets are shown in Fig. 2. The release profile obtained after chewing are a proof of the efficiency of this dosage form, as the DXM content in the residual gum decreased by increasing the mastication time for all the formulae. These results provide a proof that this dosage form is a good administration system which is able to guarantee a fast and complete drug release after a reasonable chewing time.

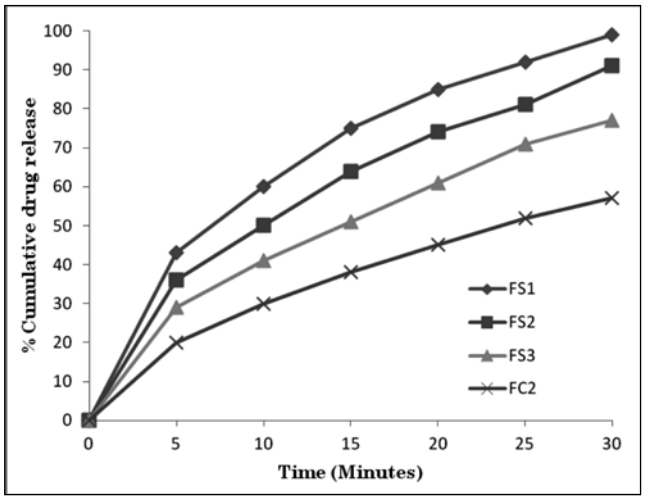

Fig. 2: Comparison of *in-vitro* drug release profile from medicated chewing gum of DXM

It is evident that the tablets containing 80% gum base concentration showed significantly higher drug release than formulations containing 90% gum base. The enhanced dissolution could be attributed to the fact that the water content of the gum base is very low and the gum binds to lipophilic substances very firmly, consequently an increase in the gum base will make the formulation more lipophilic and thereby reducing the release rate of DXM from the gummy base.

In all the cases, the R values of Higuchi matrix model were close to 1. The diffusion coefficients (n) values ranged from 0.6655 to 0.9164. Since the R values of Higuchi matrix were close to 1, the drug release follows matrix diffusion kinetics. Hence it was concluded that diffusion was the mechanism of the drug release from the medicated chewing gums. Further, observed diffusion coefficient values are indicative of the fact that the drug release from the formulation follows non-Fickian transport mechanism.

From stability studies, it was observed that the physical parameters of the formulation did not change and reproducible drug release profiles were observed.

CONCLUSION

Pharmagum M provides an excellent and compatible base with good compressibility. By incorporating the spray dried DXM granules, it was further possible to enhance the solubility and also to mask the bitter taste of the drug. The drug incorporated into the gum base in the form of spray dried granules yielded better results in contrast to the formulation containing the drug incorporated directly into the gum base. Increase in the solubility leads to enhanced dissolution rate thereby enabling us to achieve enhanced bioavailability.

It can be therefore concluded that DXM built on Pharmagum M base can be considered as a better formulation for buccal drug delivery system with the drug getting absorbed across the buccal mucosa, reaching the systemic circulation via jugular vein. To conclude, it can be said that medicated chewing gum as buccal drug delivery system can be considered as a novel drug delivery for administration of DXM, avoiding first-pass effect, reducing the risk of over dosing, with ease of administration and faster onset and action.

ACKNOWLEDGEMENTS

The authors wish to thank Mr. Sanjay Rangadhol, Director, Commercial Drug Development, SPI Pharma Inc., 21-B, Veerasandra Industrial Area, Bangalore – 560 100 for permitting us to avail usage of Erweka DRT chewing apparatus and for gifting us with Pharmagum M chewing gum base sample for carrying out the research work.

REFERENCES

1. Chewing gum, medicated.: Directorate for the quality of medicines of the council of Europe. **European Pharmacopoeia** 7th edition Strasbourg Cedex, France. 2010; 1: 709.
2. Abelson D.C., Barton J., Mandel I.D.,: The effect of chewing sorbitol-sweetened gum on salivary flow and cemental plaque pH in subjects with low salivary flow. **J Clin Dent**. 1990; 2: 3–5.
3. Woodford D.W., Lesko L.J.: Relative bioavailability of aspirin gum. **J Pharm Sci.** 1981; 70: 1341–1343.
4. Bousquet E., Tirendi S., Bonina F.P., Montenegro L., Bianchi A., Ciampini N.,: Bioavailability of two formulations of acetylsalicylic acid gums. **Pharmazie.** 1992; 47: 607–609.
5. Christrup L.L., Bonde J., Rasmussen S.N., Rassing M.R.: Relative bioavailability of (+/-)-verapamil hydrochloride administered in tablets and chewing gum. **Acta Pharm Nord.** 1990; 2: 371–376.
6. Benowitz N.L., Jacob P., Savanapridi C.: Determinants of nicotine intake while chewing nicotine polacrilex gum. **Clin Pharmacol Ther.** 1987; 41:467–473.
7. Davoli E., Stramare L., Fanelli R., Diomede L., Salmona M.: Rapid solid-phase extraction method for automated gas chromatographic-mass spectrometric determination of nicotine in plasma. **J Chromatogr B Biomed Sci Appl.** 1998; 707: 312–316.
8. Pedersen M., Rassing M.R.: Miconazole and Miconazole nitrate chewing gum as drug delivery systems - a practical application of solid dispersion technique. **Drug Dev Ind Pharm.** 1990; 16(1): 55-74.
9. Andersen T., Hansen M.G., Pedersen M., Rassing M.R.: Chewing gum as a drug delivery system for nystatin. Influence of solubilising agents upon the release of water insoluble drugs. **Drug Dev Ind Pharm.** 1990; 16(13): 1985-1994.
10. Pandey S., Goyani M., Devmurari V.: Development, In-*Vitro* Evaluation and Physical Characterization of Medicated Chewing Gum: Chlorohexidine Gluconate. **Der Pharmacia Lettre.** 2009; 1(2): 286-292.
11. Upendra R.M., Prasanthi G., Ramesh Y.: Formulation and evaluation of medicated chewing gum of Promethazine hydrochloride. **Journal of Pharmacy Research**. 2011; 4(9): 3247-3250.
12. Rassing MR.: Chewing gum as drug delivery system. **Adv Drug Deliv Rev.** 1994; 13: 89–121.
13. Mikos A.G., Nikolaos A. Peppas.: Bioadhesive analysis of controlled-release systems. IV. An experimental method for testing the adhesion of microparticles with mucus. **J Controlled Release.** 1990; 12(1): 31-37.
14. Christrup L.L., Angelo H.R., Bonde J., Kristensen F., Rasmussen S.N.: Relative bioavailability of methadone hydrochloride administered in chewing gum and tablets. **Acta Pharm Nord.** 1990; 2: 83–88.
15. Rindum J.L., Holmstrup P., Pedersen M., Rassing MR., Stoltze K.: Miconazole chewing gum for treatment of chronic oral candidosis. **Scand J Dent Res.** 1993; 101: 386–390.
16. Yamini M., William J.I., Paul X.B., Rick S.C., Barbara R.C.: *In vitro* release of nicotine from chewing gum formulations. **Dissolution Technol.** 2004; 11: 12-15.
17. Kukanich B., Papich M.G.: Plasma profile and pharmacokinetics of dextromethorphan after intravenous and oral administration in healthy dogs**. J Vet Pharmacol Ther**. 2004; 27(5): 337-41.
18. Malladi M., Kanti R., Nair R., Wagh S., Padakanti H., Mateti A.: Design and evaluation of taste masked dextromethorphan hydrobromide oral disintegrating tablets. **Acta Pharm.** 2010; 60: 267–280.
19. Pongjanyakul T., Prakongpan S., Rungsardthong U., Chancham P., Priprem A.: Characteristics and *in vitro* release of Dextromethorphan resonates. **Powder Technology.** 2005; 152: 100-106.
20. Kulkarni G.S., Sateesh Babu P.R.: Design and evaluation of tizanidine buccal mucoadhesive patches. **Journal of App. Pharm. Sci.** 2012; 2(4): 74 – 81.
21. Pandit A.P., Joshi S.B.: Formulation development of chewing gum as a novel drug delivery system for diltiazem hydrochloride. **Indian Drugs.** 2006; 43(9): 724-728.
22. Marques M.R.C., Loebenberg R., Almukainzi M.: Simulated biological fluids with possible application in dissolution testing. **Dissolution Technologies.** 2011; August: 15-28.
23. Bhowmik D., Chiranjib B., Krishnakanth., Pankaj., Chandira R.M.: Fast dissolving tablet: an overview. **Journal of Chemical and Pharmaceutical Research.** 2009; 1(1): 163-177.
24. Swamy N.G.N., Dharmarajan T.S., Paranjothi K.L.K.: Study of the binding properties of hydroxypropyl guar and its utilization in the formulation and evaluation of metoprolol tartarate tablets. **RGUHS J Pharm Sci.** 2012; 2(1): 45-54.
25. Dextromethorphan Hydrobromide.: The united States Pharmacopeial Convention. **United States Pharmacopoeia.** USP-34. 2011; 2525-2526.

26. Morjaria Y., Irwin W.J., Barnett P.X., Chan R.S., Conway B.R.: In vitro release of Nicotine from chewing gum formulations. **Dissolution Technologies.** 2004; 5: 12 – 15.

27. Kvist C., Andersson S.B., Fors S., Wennergren B., Berglund J.: Apparatus for studying in vitro drug release form medicated chewing gums. **Int J Pharm.** 1999; 189: 57-65.

28. Swamy N.G.N., Rupa V., Abbas Z., Dasankoppa FS.: Formulation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble Mebendazole. **Indian Drugs.** 2010; 47(9): 47-54.

29. Swamy N.G.N., Abbas Z., Preparation and *in vitro* characterization of mucoadhesive polyvinyl alcohol microspheres containing Amlodipine Besylate for nasal administration. **Ind J Pharm Edu Res.** 2012; 46(1): 52-58.