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PROSPECTIVE ACTION PLAN ON DEVELOPMENT OF GASTRO RETENTIVE FLOATING TABLETS

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ABSTRACT

The work projects prospective action plan to be following while developing gastro retentive floating tablets (GRFT). Research in said field aimed for combating drawback of short gastric residence time (GRT) and unpredictable gastric emptying time (GET), associated with oral drug delivery systems. These systems retard their gastric emptying time and improve gastric residence time. They improve patient compliance and are convenient one, thus preferred. Development of product is aiming to have process that ensures acceptable and reproducible product quality and performance throughout shelf life and life cycle. This seems to be difficult task, which requires proper planning with extensive knowledge. Scarce publications are available in this field. The manuscript will aid researchers while planning for designing a robust GRFT.

KEY WORDS: action plan, development, gastro retentive, floating tablets, prospective.

INTRODUCTION

Orally administered dosage forms preferred from long age. Their performance and success being limited by drug releasing pattern, GRT, and GET. Short GRT, and variable and unpredictable GET diminishes their efficacy. These are of prime concern for drug with narrow absorption window and those intending controlled or sustained release. [1-6]

Said problem can be overcoming with gastro retentive dosage forms (GRDFs). These remain in upper part of the GI tract for extended period, against all physiological barriers. They releases drug in a controlled manner and finally exit out of body. Besides they can be

resulting drug targeting, minimises drug waste, improves bioavailability, and address regional variability in drug absorption in the intestine. [7- 12]

GRDFs resulting with assorted approach. They may high-density system, magnetic system, floating system, mucoadhesive system, expandable system, superporous hydrogels, or dual working systems. [2, 3] Each class of GRDFs have inherent processing technicalities, utility, and limitations. These facts create ambiguities while selecting an appropriate system for selecting process and formula of GRFT. [13, 14]

Said facts necessitates for having literature on prospective action plan for development and design of GRFB. Knowledge on exploitable system is prerequisite. Presented information will help researches while designing a robust GRFB with wished performance.

GASTRO RETENTIVE TABLETS

GRFT are ptarticulate or non-particulate single or multiple unit system. These are suitable for drugs acting locally in stomach and duodenum, having site-specific absorption limitations, getting primarily absorbed in stomach or duodenum, degrading in colon, and so on. These will be advantageous for drugs intending to act locally on gastric mucosa of stomach. They will be valuable in treatment of peptic ulcer and gastritis, and vigorous intestinal movement conditions linked with certain type of diarrhoea. [2-7]

Advantages: Retains drug in stomach, minimises their degradation in colon, and improve bioavailability of many drugs. [2-7]

Limitations: Unsuitable for drugs that are insoluble or unstable in gastrointestinal (GI) tract, irritate gastric mucosa, undergo first pass metabolism, or require release in colon. Un-wiser for drugs, that was getting absorbed throughout GI tract. Major limit is requirement for high level of fluid in stomach and patient had to remain in upright condition. [2-7, 9, 15]

APPROACHES OF DESIGN OR DEVELOPMENT

Several approaches exploited for designing GRTB. Figure-1 depicts classes of important approaches followed in formulating them, which are as follows. [2-8, 16, 17]

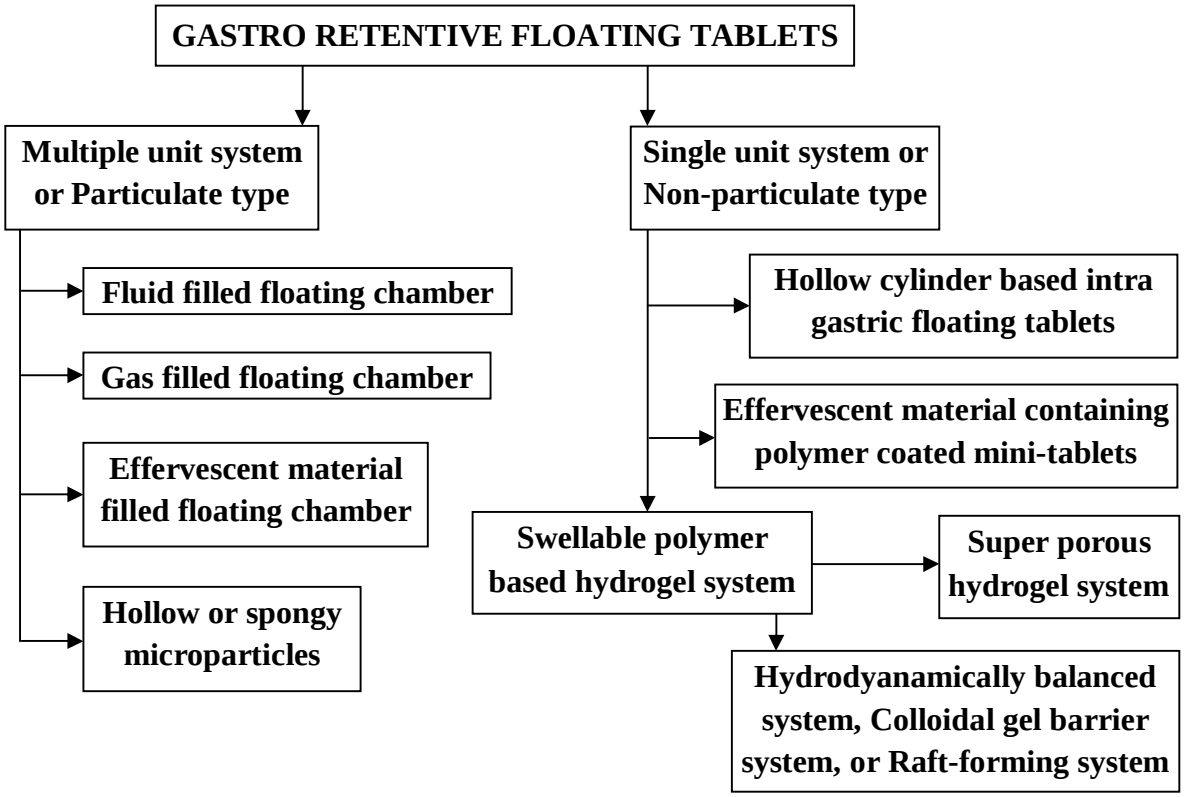

Fig. 1 Classification of gastro retentive tablets

This system has bulk density lower comparing gastric content (1 g/cm^3) and immediate buoyancy. They remain buoyant in stomach for extended period without affecting gastric emptying rate. In floating state, they releases drug slowly and after being exhaust from the drug their residual system emptied from stomach. Major drawbacks are requirement for high level of fluid in stomach and patient had to remain in upright condition. [5, 9, 15]

These tablets are single or multiple unit system of particulate or non-particulate type and can be developing as single layer to multilayer tablets. Single unit systems based on non-particulate system while multiple unit system is particulate one. Non-particulate one uses low-density polymer to get the globular shells, a drug carrier or release controlling system. Particulate systems are matrix, sponge, or hollow microparticles with or without inbuilt air or gas trapping vessel or system. Matrix system based particulate type is bioadhesive and/or effervescent system. Gas-/Fluid-filled floating chamber based system have microporous component that houses drug reservoir and gas-filled floatation chamber. GI fluid enters drug reservoir through microporous membrane to dissolve and subsequently release them. [3-5, 18]
Multi-particulate system are advantageous than single unit systems, and used mostly. They provides more predictable release profile, lowers probability of failures and dose dumping,

allows co-administration of incompatible substances or units with different release profiles, and improves margin of safety along with reliability and performance. Multiple units were formulated from low-density materials and/or by entrapping oil, air, or gas. Muulti-particulate system may contain mucoadhesive microparticles. [3-5, 19, 20]

Single unit systems either mucoadhesive system, swellable system, or hydrodynamically balanced systems (HBS). Synonym of HBS is colloidal gel barrier system, or raft-forming systems. HBS contains high level of one or more highly soluble gel forming cellulosic hydrocolloids and matrix-forming polymer. Exploited gel forming polymers are hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, polysaccharides, agar, sodium alginate, and so on. Exploited matrix-forming polymers are polycarbophil, polyacrylate, polycarbonates, polystyrene, polymethacrylate, polyethylene oxide, polyvinyl acetate, and so on. These upon contact with gastric fluid hydrate up and forms colloidal gel barrier around its surface. [3, 21]

Mucoadhesive system employs natural or synthetic mucoadhesive polymer. These upon disintegration bind to the gastric epithelial cell surface or mucin and increases GRT. Their effectiveness in acidic environment and high turnover of mucus remain unaddressed. [3, 6, 7, 21, 22]

PROSPECTIVE ACTION PLAN OF DEVELOPMENT

Effervescent, bioadhesive, or and swellable type of GRFT can be prepared with particulate and non-particulate system. Their matrix-particulate type contain microparticle (having ability to float) along with excipients, while matrix-non-particulate involves mechanisms like swelling or mucoadhesion of polymer. Their matrix type may be effervescence and non-effervescence system. [3, 9, 19, 23-28]

GRFT are prepared with polymeric excipients like hydroxypropyl cellulose, crospovidone, sodium carboxy methylcellulose, ethyl cellulose, HPMC, and so on. Wettability of drugs can be improving by inclusion of sodium lauryl sulphate and HPMC, which resulting uniform drug release. Quantity and quantity of polymer, and plasticiser–polymer ratio monitors buoyancy and drug release profile of GRFT. [3-5, 21]

Matrix-particulate type requires spherical microparticles (microballoon, floating microparticle, and so on). Microparticles can be prepared from albumin, polymethacrylate,

starch, polyacrylamide, gelatine, chitosan and polyalkylcyanoacrylate, cellulose acetate autyrate (M.W. of 16,000) and eudragit RL 100 (M.W. of 150,000), and so on. [19, 24]

Floating microparticle requires pours or spongy polymeric or non-polymeric system. Hollow or spongy microparticle can be prepared with mucoadhesive or non-mucoadhesive polymer. Those prepared with mucoadhesive polymer will synergize GRT. [23, 29-31]

Hollow microparticles should inbuilt with central hollow space, behave like microballons, and have floating properties. [19, 23, 25, 26, 31, 32] Quality and quantity of polymer, and ratio of plasticiser to polymer should be of appropriate for achieving desired drug release profile and buoyancy. [28, 32-34]

Spongy microparticle has to contain microporous component as drug reservoir and enveloping floatation (inflatable) chamber. Floatation chamber or gas compartment should be filling with suitable air, gas, or volatile liquid or solid with inertness. Top and bottom walls of which must contain apertures or openings for entry of gastric fluid to dissolve and release drug. Other two walls have to seal for preventing leakage of dissolved or un-dissolved drug. [28, 34]

Gas compartment be filling with suitable gases like cyclopentane, diethyl ether, etc. in solid or liquid state. Alternately, effervescent system can be substitute for these gases. Effervescent system be having drug carrier matrix surrounded by double layers. Inner layer be comprise an inner sub-layer containing bicarbonate salts and an outer sub-layer containing organic acids without direct contact. The outer layer should act as swellable membrane layer. Floating type ion exchange resin beads generating CO_2 upon interaction with gastric fluid can be substitute for gases. [18, 33-36]

The gas compartment has to plug with a bioerodable polymer that must permit escape of vapour and consequently facilitating exit of system from the stomach. After swallowing, liberated microparticles of GRFT should evaporate the volatile liquid or solid of gas compartment, or should liberate CO_2 from effervescent system, and form swollen pills (microballoons) for floatation. [5, 28, 34, 36]

Swellable type should contain a gel forming or highly swellable cellulose type hydrocolloids or polysaccharides and a matrix forming material. Upon swallowing they be imbibing with gastric fluid and should swell up unrestrained to an extent where their exit from stomach

being prevented. Swollen polymer should maintain relative integrity within outer gelatinous barrier. To confer buoyancy the outer gelatinous barrier should entrap air. Their performance is being improving through incorporation of hydrophilic particulate materials (e.g. croscarmellose sodium) in formulation, which results superporous hydrogels. These hydrogels should have average pore size more than 100 µm and ample mechanical strength for withstanding gastric contraction. [37, 38]

HBS is a modified version of swellable type. These should contain drug, gel-forming hydrocolloids, effervescent compounds, and matrix-forming polymer. Effervescent compounds like bicarbonate salts and organic acid (tartaric or citric) being use. Upon oral ingestion of HBS, the system should have ability to encounter gastric fluid, hydrate the hydrocolloids, form a colloid gel barrier around its surface, and liberate CO_2. Liberated CO_2 in consequence be entrapping in swollen hydrocolloid gel barrier. Resultant gel barrier be have lower bulk density comparing gastric fluids. [5, 39-41]

HBS based GRFT be grooming as single/bi/tri-layer tablet. Single-layered one should be formulating by compressing drug and gas generating components in hydrocolloid containing layer. Bi-layered tablet being obtain by compressing gas generating components in hydrocolloid containing layer and drug in other layer. Tri-layered one is obtainable by compressing gas-generating components in hydrocolloid containing layer and incompatible drugs in second and third layers. Bi/tri-layered tablet be selecting for incompatible drugs, and multiple drug regimen or extended release product. [3, 13, 39-45]

Mucoadhesive based single unit matrix type should contain mucoadhesive polymers. Exploitable mucoadhesive polymers are chitosan, HPMC, carbopol, lectins, polycarbophil, carboxy methylcellulose, gliadin, ion exchange resins, and so on. These be preparing as particulate-matrix or non-particulat-matrix type. Particulate type be compressing from the blend of excipients and drug (as mucoadhesive microspheres). Non-particulat-matrix type of these upon swallowing should swell up and/or adhere with mucous lining of GI tract. Their effectiveness in acidic environment and high turnover of mucus requires redressing. [6, 7, 21, 22, 42-45]

Single unit system is developing with popcorn, poprice and polystyrol as drug carriers. Desired release profile can be achieving through their subsequent coating with polymers like hydroxycellulose, ethyl cellulose, methacrylate, cellulose acetate phthalate, etc. [3, 6, 21]

Hollow cylinder based system be enclosing an air-filled space within hollow polypropylene cylinder and each end of cylinder be sealing with matrix tablet. Overall density of GRFT must be resulting floatation of it, until at least one of tablets has dissolved. [41] Alternately polymer coated mini-tablets (behaving like microballoons) containing effervescence system can be formulated. In such tablets, the drug and the bicarbonate to be loaded on separate ion exchange resins. The bicarbonate resin beads subsequently coated with a semi permeable membrane to restrain rapid loss of CO_2. After exposure to gastric media, exchange of bicarbonate and chloride ions should take place for generating CO_2, which will get trap within membrane. [14, 22-26, 30, 34]

GRFT should be evaluated for various parameters namely floating-time, buoyancy capabilities, specific gravity, swelling or water uptake study, content uniformity and drug content, mechanical properties, hardness and friability, *in vitro* release and release kinetic, and so on. [1, 3, 24, 32, 46, 47] Microparticles of multi-particulate system evaluated for particle shape, particle size and size distribution, surface morphology, ^{1}H- and ^{19}F-MRI technique, and x-ray diffraction studies, and so on. [1, 3, 24, 32, 46, 47] Physico-chemical interactions of drug(s) and excipients should be examining. This should be studied with fourier transforms infrared spectroscopy, powder X-ray diffraction, differential scanning calorimetry, and so on. *In vivo* performance study, gastroretentivity study, stability study, and *in vivo-in vitro* correlation study has to done and results should be evaluating, statistically. [1, 3, 48-52]

CONCLUSION

For GRFT be successful, detailed understanding of physiochemical properties of drug, physiological events of drug in the GI tract, impact of GI tract physiology on drug delivery, and formulation strategies and their evaluation is requirement. *In vitro* and *in vivo* performances should be correlating along with estimating effects of simultaneous presence of food and complex motility of stomach. Sophistication of technology will ensure development of large number of GRFT with wished performance. It will optimise delivery of drug having regional absorption variability within the GI tract.

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